Genomic Profiling in Patients With Malignant Peripheral Nerve Sheath Tumors Reveals Multiple Pathways With Targetable Mutations

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Abstract

Background: The aim of this study was to determine the frequency of alterations in *BRAF* and other *RAS/RAF* genes, as well as other targetable pathways in malignant peripheral nerve sheath tumors (MPNSTs). **Patients and Methods:** Pathology specimens were available for 2 cohorts: (1) patients with MPNST at Swedish Cancer Institute (n=17) from 2004 through 2016, and (2) patients with MPNST evaluated for >300 genomic alterations at Foundation Medicine from 2014 through 2016 (n=186; including 2 Swedish patients with *BRAF*-mutated MPNST). **Results:** Of 201 MPNSTs, 13 (6.5%) demonstrated *BRAF* alterations. In the Foundation Medicine cohort, 10 of 84 tumors (11.9%) with no *NF1* alterations had *BRAF* mutations (5 were V600E, 5 other), as did 3 of 102 (2.9%) tumors with *NF1* alterations (1 V600E, 2 other). In the Foundation Medicine cohort, 47% of patients had an alteration in at least one other gene in the *RAS/RAF* pathway (not including *NF1* or *BRAF*); 46% had alterations in the PI3 pathway, with 70% having alterations in at least 1 of the 2 pathways; 57% had a *CDKN2A* alteration (80% in *BRAF*-mutated and 71% in *NF1*-altered patients); and 70% had an alteration in DNA repair genes. MPNST, both *NF1* wild-type and *NF1*-mutated, often harbor alterations in the *RAS/RAF* pathway as well as changes related to DNA repair and *CDKN2A/B*. V600E and other mutations occur in *BRAF*, suggesting the need for second-generation activating *BRAF* inhibitors. The concurrence of *BRAF* and/or *NF1* alterations with *CDKN2A/B* mutations, in particular, may be significant in the transformation of neurologic tumors from benign to malignant. **Conclusions:** All MPNSTs would benefit from a comprehensive genomic analysis. Treatments targeted to *RAS/RAF*, DNA repair, and *CDKN2A/B* pathways should be used and/or developed to treat this uncommon tumor.

J Natl Compr Canc Netw 2018;16(8):967–974
doi: 10.6004/jnccn.2018.7033

Malignant peripheral nerve sheath tumors (MPNSTs) are rare tumors for which no established systemic treatment exists. MPNSTs occur in approximately 10% of patients with neurofibromatosis type 1, with malignancy usually present in the third or fourth decade of life.¹ When MPNSTs occur sporadically in the absence of neurofibromatosis, they tend to present later in life, usually in the sixth or seventh decade, and often without an inactivating alteration in neurofibromin (*NF1*), which is seen in patients with neurofibromatosis type 1. Wild-type *NF1* protein exhibits an inhibitory

effect on the *RAS/RAF* pathway. Such tumors exhibit increased activity in the *RAS/RAF* pathway by the lack of negative feedback.² Alterations in the *PI3K/PTEN/AKT* pathway can also affect *RAS/RAF* activity³ and can be stimulated by similar stimuli as the *RAS/RAF* pathway.

Previously, we reported on a patient with a sporadic MPNST, whose tumor featured a *BRAF* V600E mutation.⁴ This mutation results in activation of *BRAF*, leading to increased activity of the *RAS/RAF* pathway.⁵ This patient had a dramatic response to vemurafenib, an

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Submitted December 23, 2017; accepted for publication April 11, 2018.
Drs. Ross, Ali, and Millis are employees of Foundation Medicine, Inc. Drs. Ali and Ross have equity interest in Foundation Medicine, Inc. The remaining authors have disclosed that they have no financial interests, arrangements, affiliations, or commercial interests with the manufacturers of any products discussed in this article or their competitors.

This study was supported in part by the Kaplan Cancer Research Fund.
Author contributions: Study concept and design: Kaplan, Ali, Millis. Development and methodology: Kaplan, Millis, Rostad. Data analysis and interpretation: Millis. Manuscript preparation: All authors. Critical revision: All authors.
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inhibitor of *BRAF* V600E. As a result, in the current study we analyzed the presence of *BRAF* alterations, other *RAS/RAF* alterations, and other genomic alterations in all MPNSTs studied at Swedish Cancer Institute and Foundation Medicine during the past 12 years.

Patients and Methods

Patients from the Swedish Cancer Institute pathology archives were identified under an Institutional Review Board (IRB)–approved protocol (No. SWD5531S-14). MPNSTs were studied using the QIAGEN QIAamp DNA FFPE Tissue Kit and *BRAF* mutation was analyzed using a laboratory-developed, allele-specific, real-time PCR assay to detect the major *BRAF* mutations; less common alterations, fusions, and large insertions/deletions are not identified by this assay. Patients from the Foundation Medicine archives underwent genome testing as previously reported.^{6,7} The *NF1* gene was interrogated for all 4 classes of alterations: single-base changes, copy number amplification, rearrangements, and large insertions/deletions (up to ~25 base changes) across all exons; sporadic versus neurofibromatosis-associated MPNST status was not evaluated. *BRAF* alterations were identified across all 4 classes of alterations and all exons. Approval for the Foundation Medicine cohort, including a waiver of informed consent and HIPAA waiver of authorization, was obtained from the Western IRB (Protocol No. 20152817). Clinical treatment and outcomes were not available for the Foundation cohort. However, pathology specimens from all *BRAF*-altered tumors were further reviewed and shown to be weakly S100-positive, melanin-negative, and HMB45-negative; none exhibited hypermutation. The 2 patients from the Swedish cohort with *BRAF* mutations received complete genomic analysis at Foundation Medicine and are included in the analysis of the Foundation cohort.

Results

A total of 201 patients with MPNSTs were included in this study, 17 of whom were identified at Swedish Cancer Institute; of these patients, 2 had *BRAF* alterations and were studied more extensively at Foundation Medicine.

Among the 186 MPNSTs profiled at Foundation Medicine (Table 1), 102 showed *NF1* alterations (55%) and 84 were *NF1* wild-type (45%). Of the patients with *NF1* wild-type MPNST, 10 of 84 (12%) exhibited *BRAF* alterations. Of the 10 *BRAF* alterations, 9 were known to be pathogenic, including 5 *BRAF* V600E, 1 R389C, 1 I710fs*24, and 2 rearrangements (see supplemental eAppendix 1 for references, available with this article at JNCCN.org). One (P341I) was of unknown functionality. Among 102 patients with *NF1* alterations, 2 exhibited likely pathogenic *BRAF* mutations, R389C and A762V, and one exhibited a functionally unknown G652E alteration.

Of the Foundation Medicine cohort, 46% of patients had alterations in the PI3 pathway (only pathogenic mutations were counted), 57% had *CDKN2A* alterations, and 70% had an alteration in DNA repair genes. The cohorts of 102 *NF1*-mutated patients and 84 *NF1* wild-type patients analyzed at Foundation Medicine were compared, with separate breakout of the 10 *BRAF*-altered cases. Differences in alteration rates were evident (Figures 1 and 2). Of note, *CDKN2A* was altered at a significantly higher rate in *NF1*-altered and *BRAF*-altered tumors versus non-*NF1/BRAF* (71%, 80%, and 34%, respectively). Rates of *TP53* (32% of *NF1*, and only 14% of

Table 1. Relationship Between *BRAF* Mutation and *NF1* Status (N=186)^a

<i>NF1</i> Status	<i>BRAF</i> Alterations	Functional Status ^b
Wild-type (n=84)	V600E, n=4	Pathogenic
	V600E and exon duplication, n=1	Pathogenic
	P341I, n=1	Unknown significance
	Rearrangement, n=2	Pathogenic
	I710fs*24, n=1	Pathogenic
	R389C, n=1	Likely pathogenic
<i>NF1</i> alteration, somatic or germline (n=102)	R389C, n=1	Likely pathogenic
	A762V, n=1	Likely pathogenic
	G652E, n=1	Unknown significance

^aIncludes only patients whose tissue was submitted for comprehensive genomic profiling at Foundation Medicine (2 from the Swedish cohort and 184 others).

^bFunctional status identified through several databases, including COSMIC, 1000 Genomes Project, dbSNP, and ExAC (to filter out common germline variants). Published literature and conference proceedings were also used to assess functional significance of variants, adjusting default rules as needed to reflect whether a variant is likely pathogenic.

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Figure 1. Comparison of frequency of top 50 genes altered in malignant peripheral nerve sheath tumor cases in the cohort analyzed at Foundation Medicine, with separate breakout of the *BRAF* and *NF1*-altered cases. Abbreviation: WT, wild-type

non-*NF1* and 13% of *BRAF*), *SUZ12* (20% of *NF1*-altered, 13% of *BRAF*-altered, 9% of non-*NF1*/non-*BRAF*-altered), and *EED* (8% of *NF1*-altered, 13% of *BRAF*-altered, 3% of non-*NF1*/non-*BRAF*-altered) also varied with subtype.

Across the entire Foundation Medicine MPNST cohort, 47% of tumors had an alteration in at least one other gene in the *RAS/RAF* pathway (*ERBB2*, *ERBB3*, *ERBB4*, *KRAS*, *MET*, *HRAS*, *MAP2K1*, *MAP2K2*, *NRAS*), not including *NF1* or *BRAF*. By group, 52% of *NF1*-altered, 50% of *BRAF*-altered, and 38% of non-*NF1*/*BRAF*-altered had at least 1 *RAS/RAF* alteration (Figure 2). Most of the alterations in the *RAS/RAF* pathway are known alterations, for which targeted therapies have been associated with positive responses in other cancers. Among tumors with alterations in the *PI3* pathway (*AKT1*, *AKT2*, *FBXW7*, *INPP4B*, *MTOR*, *PIK3C2B*, *PIK3C2G*, *PIK3C3*, *PIK3CA*, *PIK3CB*, *PIK3CG*, *PIK3R1*, *PIK3R2*, *PTEN*, *RIC-TOR*, *STK11*, *TSC1*, or *TSC2*), those with *NF1* mutations had almost 2.5 times as many alterations

in this pathway as those with non-*NF1*-altered; 70% of patients' tumors had alterations in at least 1 of the 2 pathways. Alterations in DNA repair genes (*ATM*, *BARD1*, *BRCA1/2*, *FANCA*, *PBRM1*, *CHEK2*, *MSH2*, *MSH3*, *MSH6*, *NBN*, *PBRM1*, *POLE*, *RAD51*, *RAD51C*) were found equally in 70% of tumors across subgroups.

Other altered genes identified that might inform targeted therapy included *KDR*, *KIT*, *PDGFR*, and *FGFR1* (7% each) and *NTRK1* and *FGFR2* (5% each) (see supplemental eAppendix 2 for references).

The specific *NF1* alterations in the Foundation Medicine cohort were further evaluated for frequency of specific alterations (Table 2). Notably, 2 cases harbored 4 *NF1* alterations each; 14 tumors had >1 *NF1* alteration.

Case Reports of Patients From the Swedish Cohort

Patient 1 was a 51-year-old woman who presented with an MPNST. Her initial presentation and treat-

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Figure 2. Ratio of patients in the Foundation Medicine cohort with malignant peripheral nerve sheath tumors exhibiting alterations in key pathways.
*Statistically significant difference between subtypes ($P<.0001$).
**Statistically significant differences between *BRAF/NF1* wild-type (WT) and *NF1*-altered tumors ($P<.0001$).

ment were previously reported,⁴ including a detailed pathologic description and clinical photographs documenting response. The present study provides details of further follow-up. She presented with a large, high right axillary mass. The tumor was intimately associated with the brachial plexus. She was treated with surgical removal and postoperative radiation therapy. Nine months later she developed a recurrence on the contralateral shoulder, which was also removed and radiated. This tumor was found to have a *BRAF* V600E

mutation. No clinical or genomic evidence of neurofibromatosis was seen. Shortly thereafter the patient developed widespread bulky metastatic disease. She had a transient modest response to sorafenib but a dramatic almost complete response to vemurafenib that lasted 4 months. At that time, she developed progressive disease. A second biopsy demonstrated a *BRAF* kinase domain (*BRAF*-KD) duplication.⁸ Therapy was discontinued for 1 month, followed by re-treatment with vemurafenib, this time with the addition of trametinib. She had a very good partial response, which lasted for 3 months. On disease progression, she was treated with vemurafenib plus everolimus without response. She experienced a 4-month partial response to carboplatin (her tumor was also *BRCA2*-mutated), but then developed progressive disease and died from her MPNST.

Patient 2 was a 58-year-old woman with a history of neurofibromatosis with multiple subcutaneous tumors. She developed a large tumor in the subcutaneous tissues of the occipital region. An 8-cm MPNST was surgically removed. Multiple nodules were present in the resection, which represented the benign plexiform neurofibroma characteristic of neurofibromatosis. Superimposed were varying degrees of malignant involvement by MPNST spreading within the confines of the perineurium of the plexiform neurofibroma. At its maximal involvement, the sarcoma was composed of a highly cellular population of monomorphous cells, which stained positively for S100. Sox 10 and p16 showed diffuse positive staining. *BRAF* V600E was detected in the malignant tumor. Analysis at Foundation Medicine revealed another *BRAF* alteration, which was identified at a very low frequency in a homopolymer repeat region of the gene, and could not be excluded as an artifact. Loss of *CDKN2A/B* was also detected. Focal areas of necrosis were seen. The Ki-67 labeling index was moderately elevated to 21%, in contrast to nearly 0% in the benign neurofibromatosis regions. Tissue obtained from the neurofibroma at that time did not harbor either mutation. The sarcomatous component did not show extension to the soft tissue margins and was rather confined to the scaffolding of the plexiform neurofibroma. The peripheral nerve margins, however, showed, in addition to benign neurofibroma, rare pleomorphic and Ki-67 positive nuclei, consistent with extension of the sarcoma to the nerve margins. Because of the positive surgical

Table 2. Frequency of Specific <i>NF1</i> Alterations in the Foundation Medicine Cohort			
Frequency	Protein Effect	Known Pathogenic?	Alteration
11	Deletion	Known	CN
8	Truncation	Likely	RE
4	Rearrangement	Unknown	RE
3	q514fs*43	Known	SV
3	r1534*	Known	SV
3	r1276*	Known	SV
2	q400*	Known	SV
2	r2258*	Likely	SV
2	Splice site 7190-1g>a	Likely	SV
2	y80*	Likely	SV
2	q519*	Likely	SV
104	All different sites, spanning length of protein	15 known, 68 likely, 21 unknown	103 SV, splice site, or frame shift; 1 amplification

Abbreviations: CN, copy number change; RE, rearrangement; SV, single base variation.

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margin, the patient subsequently received 6,000 Gy of radiation therapy to the area. With 3 years' follow-up, no recurrence of this tumor has been seen. At 34 months after the appearance of the MPNST, the patient developed another large tumor mass, which on surgical removal demonstrated plexiform neurofibroma with focal atypia. She has received no further treatment for her disease at this time.

Discussion

MPNSTs are uncommon, occurring in approximately 1 in 10 million patients per year.^{9,10} They can sometimes be treated with local therapy, including surgery and radiation. However, these tumors can metastasize and be very aggressive, with an average long-term survival of only 20% to 50%. The SARC006 trial reported that systemic chemotherapy with drugs used for sarcoma, such as doxorubicin, ifosfamide, and etoposide, produced approximately a 25% objective response rate, but these responses have not been durable.¹¹ Trials with a variety of targeted agents are underway. Some responses have been reported with imatinib, an inhibitor of *cKIT*, but no clearly dramatic activity has been reported thus far.¹⁰ Therefore, new systemic treatments are sorely needed.

Approximately 50% of MPNSTs are considered to be derived from neurofibromas and possess an inactivating mutation in *NF1*, which would likely lead to increased *RAS/RAF* activity. Because alterations in the *PI3K/PTEN/AKT* pathway can also affect *RAS/RAF* activity, alterations in these pathways were also evaluated. In this series, *PI3K* alterations were significantly more common in *NF1*-altered versus *NF1* wild-type tumors. During review, alterations in the DNA repair pathways were also identified frequently, suggesting that inability to correctly repair DNA damage caused an additive effect in malignancy. *CDKN2A/B* mutations were also extremely frequent, particularly in *BRAF*-mutated tumors.

Four other studies have reported activating *BRAF* V600E mutations in MPNST (Table 3).^{12–15} Combining these studies with our own (including the entire Swedish cohort), 20 of 351 patients (5.7%) with MPNST demonstrated *BRAF* alterations, of which 12 of 351 (3.4%) were the classic V600E mutation. In our study of the patients more fully analyzed at Foundation Medicine, 11.9% of *NF1* wild-type MPNSTs harbored *BRAF* alterations, 5 of which were classic

Table 3. Literature Review of *BRAF* V600E Mutations in Malignant Peripheral Nerve Sheath Tumors

Reference	Patients, N	All <i>BRAF</i> Mutations, n	V600E Mutations, ^a n
Schindler et al ¹³	18	0	0
Botillo et al ¹⁵	47	1	1
Je et al ¹⁴	24	0	0
Hirbe et al ¹²	61	6	6
Kaplan	201	13	5
Total	351	20	12

^a*BRAF* mutations other than V600E from the current series are noted in Table 1.

V600E activations (6.0%), 4 were known or likely to be pathogenic, and 1 of unknown pathogenicity. Among *NF1*-mutated tumors, 2.9% harbored a *BRAF* mutation, 2 of which were likely pathogenic and 1 was of unknown pathogenicity. This study, in agreement with that of Hirbe et al,¹² suggests that *BRAF* alterations may be more common in patients with *NF1* wild-type versus *NF1*-mutated tumors who develop MPNSTs. It is unclear whether methods used in the prior studies listed here would have detected *BRAF* mutations other than V600E. Our results demonstrate that, although uncommon, *BRAF* mutations are common enough that they should be searched for in all patients with MPNST.

In the one patient treated with a *BRAF* V600E inhibitor in this series, a remarkable response was seen. However, it lasted only approximately 4 months. After a month off treatment, she was re-challenged with the same drug plus an *MEK* inhibitor and briefly responded again. It is possible that the level of *BRAF*-mutated cells had decreased in her tumor to preresistant levels rendering the tumor again susceptible to vemurafenib, as has been reported and reviewed in mutated melanoma studies in both animals and humans.^{16–18} It is also possible that the addition of an *MEK* inhibitor was able to partially overcome tumor resistance by blocking the *RAS/RAF* pathway further downstream.¹⁹ The combination of a *BRAF* V600E blocker and an *MEK* inhibitor has been shown to be superior to single-agent therapy in melanoma.^{20,21} Subsequent treatment of this patient with vemurafenib and everolimus, an inhibitor of the *mTOR/AKT* pathway, was not effective, despite the demonstration of compensatory amplification of this alternate pathway as another mechanism of resistance to activated *BRAF* inhibitors.⁴

Patient 1 was also found to harbor a *BRAF*-KD duplication in addition to the V600E mutation when she was rebiopsied at the time of tumor progression. This mutation was sought in her original biopsy and was not present at that time. We have recently reported the occurrence of this mutation in a variety of tumor types, including patient 1.⁸ It is possible that this mutation became as, or more, important to tumor survival than the V600E activation, and that this second mutation was partially overcome by the addition of an MEK inhibitor. Regorafenib has produced a dramatic response in one patient with this *BRAF*-KD mutation in a salivary acinic cell malignancy.⁸ The patient whose tumor harbored the fusion alteration treated with regorafenib in that study did not have the V600E mutation, suggesting that regorafenib may well be active against the kinase duplication mutation. Hutchinson et al²² also reported the development of 2 different *BRAF* fusion mutations in patients with melanoma. In that study, therapy with an MEK inhibitor in vitro was active in inhibiting tumor growth. Further, Kulkarni et al²³ described *BRAF* V600E–mutated melanoma in a patient who developed an *AGAP3*-*BRAF* fusion mutation that was resistant to vemurafenib but responded to vemurafenib plus an MEK inhibitor. After treatment was discontinued, the fusion mutation was no longer detectable, suggesting that such mutations may be clonally treatment-selected by exposure to *BRAF* inhibitors alone.

In our study, we identified a number of *BRAF* mutations in addition to *BRAF* V600E and the fusion mutation described earlier, many of which have been shown to be pathogenic ([supplemental eAppendix 1](#)). Chakraborty et al²⁴ showed in Langerhans cell histiocytosis that an additional *BRAF* fusion mutation and other small in-frame *BRAF* deletions can lead to *BRAF* activation. These tumors are resistant to traditional *BRAF* V600E inhibitors but sensitive to MEK inhibitors, as well as the second-generation *BRAF* inhibitor PLX8394. Similarly, Diamond et al²⁵ recently reported in histiocytosis that first-generation *BRAF* inhibitors are clinically effective in *BRAF* V600–mutant disease, whereas MEK inhibition was very successful against such patients harboring a variety of *BRAF* mutations, as well as altered *MAP2K1*, *MAP2K2*, *KRAS*, *CRAF*, and *ARAF*. Yao et al²⁶ have studied the mechanism of *BRAF* activation in various *BRAF* mutants. Acti-

vating *BRAF* V600 mutants are activated monomers when RAS activity is low and are inhibited by first-generation *BRAF* V600 blockers, whereas other activating *BRAF* mutants noted in their study were constitutive RAS-independent dimers. First-generation *BRAF* blockers are effective against mutant monomers but not dimers. Their binding to one site in the dimer significantly reduces their affinity for the second, rendering those mutants resistant. Alternatively, the second-generation *BRAF* inhibitor PLX8394 binds to both sites of mutant *BRAF* dimers and is active against both monomer and dimer *BRAF* mutants. Although none of the non-V600 *BRAF* mutations reported in the current study were tested by Yao et al, it will be important to explore use of this drug in such patients. A clinical trial in patients exhibiting these types of mutations is currently underway (ClinicalTrials.gov identifier: NCT02428712).

Use of MEK inhibitors is particularly interesting in patients with loss of neurofibromin activity, which results in unrestrained activity of the RAS/RAF pathway. Multiple studies have suggested loss of neurofibromin activity as a driver of growth in melanomas that can be blunted by MEK inhibitors.^{27–30} The clinical utility of MEK inhibition was confirmed in the study by Dombi et al,³¹ in which 71% of children with neurofibromatosis type 1 had clinically significant durable shrinkage of benign inoperable plexiform neurofibromas with selumetinib, a known MEK inhibitor. Whether inhibition of MEK will yield clinically significant responses in patients with somatic *NF1* mutations in MPNSTs remains to be explored. A number of compounds are in clinical development in an attempt to block this pathway further downstream at the level of ERK. Morris et al³² reported activity of one such compound even in tumors with *BRAF* V600E and MEK^{p124L} overexpression and acquired resistance to both *BRAF* and MEK inhibitors, whereas Sullivan et al³³ reported clinical activity of BVD-523 in MAPK-mutant tumors, including in patients with *BRAF* V600E and other *BRAF*-activating mutations.

The high percentage of patients who harbored at least one alteration in the RAS/RAF pathway suggests that therapy options might exist for a large subgroup of patients with MPNST, including *BRAF*-altered tumors for which we have shown response. As previously discussed, a variety of resistance mechanisms have been demonstrated either in animals or

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in vitro, suggesting that activation of other metabolic pathways can bypass the RAS/RAF pathway.^{4,5} Combining blockade of multiple interacting pathways such as RAS/RAF and PI3K/PTEN/AKT may also prove useful in the clinical setting. The other studies noted in Table 3 performed varying degrees of extensiveness of genomic testing. In particular, we have found additional *BRAF* alterations other than V600E that are pathogenic. It will be important for future studies to perform genomic evaluation of all the relevant pathways discussed.

These considerations may prove useful in multiple types of tumors. As noted, activating *BRAF* mutations and *BRAF* fusions and alterations in other pathways that impact RAS/RAF activity have been reported in many malignancies.^{8,34} In addition, multiple kinases and transcription factors are known to stimulate this pathway both under normal and malignant conditions. Some of these, such as *EGFR*, have already been shown to be important in multiple tumor types, and inhibitors of these are clinically readily available. Such inhibitors could be evaluated both alone as well as in combination with the compounds discussed.³⁵

Analysis of other pathways and driver genes identified alterations in DNA repair pathways, *CDKN2A/B*, the PI3 kinase pathway,³⁶ *KIT*, *KDR*, *PDGFR*, *FGFR1/2/3*, and *NTRK1*. The striking occurrence of *CDKN2A/B* alterations in patients with *BRAF* and *NF1* alterations may be of particular clinical significance. Studies have suggested that these 2 mutations taken together may be important in progression of pediatric low-grade glioma to secondary high-grade glioma,^{37–39} another neurologic malignancy developing from a less aggressive lesion, whereas Schiffman et al⁴⁰ noted similar findings in pediatric malignant astrocytoma. Of note, patient 2

with *BRAF*-mutated MPNST also demonstrated loss of *CDKN2A/B*. She had a nearby benign neurofibroma that harbored neither mutation. The incidence of *BRAF*-activating mutations in benign neurofibromatosis tumors is not known. However, it is known that *BRAF* mutations are often seen in benign melanocytic nevi,⁴¹ wherein *CDKN2A* alteration has been shown to be a late step in the development of malignancy.⁴² Thus, it is likely that other events besides *BRAF* activation or *NF1* deactivation, such as *CDKN2A/B* mutation, may be needed to confer malignant behavior. Indeed, Sohler et al⁴³ hypothesized this very evolution in MPNST.

SUZ12 and *EED* mutations have been previously reported in MPNSTs. These are components of the polycomb repressive complex 2 (PRC2), and loss-of-function mutations have been reported in high frequencies in these tumors, particularly in association with *NF1* and *CDKN2A* alterations.⁴⁴ Further, loss-of-function *PRC2* mutations have been associated with amplification of RAS-driven transcription and vulnerability to *MEK* and *BRD4* inhibitors.⁴⁵ Our finding of an association between *CDKN2A/B*, *BRAF*, *PRC2*, and *NF1* mutations is consistent with these studies, raising the question of a critical role in tumorigenesis.⁴³ Trials are currently underway testing the utility of clinically available CDK4/6 inhibitors against this mutation.⁴⁶

Conclusions

Comprehensive genomic evaluation of MPNSTs is warranted to identify not only *BRAF* alterations but also alterations in pathways related to RAS/RAF. The findings of frequent mutations in DNA repair genes and *CDKN2A/B* suggest additional targets for therapeutic intervention in this rare malignancy.^{47–50}

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