ORIGINAL RESEARCH

Comprehensive Genomic Profiles of Melanoma in Veterans Compared to Reference Databases

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Background: Veterans represent a unique patient population with various exposures that may predispose them to cancer. Mutational signatures associated with these exposures are described in other tumor types.
Methods: This retrospective review analyzes the comprehensive genomic profiling reports of 35 veterans with metastatic melanoma at a large US Department of Veterans Affairs medical center. The genomic findings were compared with those from the Catalogue of Somatic Mutations in Cancer and The Cancer Genome Atlas.
Results: The melanomas found in these veterans showed a significantly higher frequency of variants in *CDKN2A/B*; a significantly lower frequency of variants in *ROS1*, *GRIN2A*, *KDR*, *KMT2C* (*MLL3*), *KMT2D* (*MLL2*), *LRP1B*, *PTPRT*, *PTCH1*, *FAT4*, and *PREX2*; and a significantly higher frequency of tumor mutational burdens exceeding 10 mutations/megabase.
Conclusions: The presence of statistically significant differences between the genomic findings from the veterans' melanomas and those of general population melanomas from reference databases suggests that additional research is warranted to corroborate these differences and clarify their etiologic, prognostic, and therapeutic relevance.

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The veteran population, with its unique and diverse types of exposure and military service experiences, faces distinct health factors compared with the general population. These factors can be categorized into exposures during military service and those occurring postservice. While the latter phase incorporates psychological issues that may arise while transitioning to civilian life, the service period is associated with major physical, chemical, and psychological exposures that can impact veterans' health. Carcinogenesis related to military exposures is concerning, and different types of malignancies have been associated with military exposures.[1] The 2022 introduction of the Cancer Moonshot initiative served as a breeding ground for multiple projects aimed at investigation of exposure-related carcinogenesis, prompting increased attention and efforts to linking specific exposures to specific malignancies.[2]

Melanoma is the deadliest skin cancer, accounting for 1.3% of all cancer deaths.[3] Although it may only account for 1% to 5% of skin cancer diagnoses, its incidence in the United States' population has been increasing.[4,5] There were 97,610 estimated new cases of melanoma in 2023, according to the National Cancer Institute.[6]

The incidence of melanoma may be higher in the military population compared with the general population.[7] Melanoma is the fourth-most common cancer diagnosed in veterans.[8]

Several demographic characteristics of the US military population are associated with higher melanoma incidence and poorer prognosis, including male sex, older age, and White race. Apart from sun exposure—a known risk factor for melanoma development—other factors, such as service branch, seem to contribute to risk, with the highest melanoma rates noted in the Air Force.[9] According to a study by Chang et al, veterans have a higher risk of stage III (18%) or stage IV (13%) melanoma at initial diagnosis.[8]

Molecular testing of metastatic melanoma is currently the standard of care for guiding the use of US Food and Drug Administration-approved targeted therapies such as BRAF, MEK, and KIT inhibitors. This comparative analysis details the melanoma comprehensive genomic profiles observed at a large US Department of Veterans Affairs (VA) medical center (VAMC) and those reported in reference databases.

METHODS

A query to select all metastatic melanomas sent for comprehensive genomic profiling from the Kansas City VAMC (KCVAMC), identified 35 cases from 2019 through 2023 as the study population. The health records of these patients were reviewed to collect demographic information, military service history, melanoma history, other medical, social, and family histories. The comprehensive genomic profiling reports were reviewed to collect the reported pathogenic variants, microsatellite instability (MSI) status, and tumor mutational burden (TMB) for each case.

TABLE 1. Baseline Service, Medical, Social, and Family History by Patient

Patient	Service branch	Service era	Exposures	Family history	Primary tumor site	Tumor stage
1[a]	Marine Corps	Unspecified	None	None	Unknown	IV
2[a]	Navy	Unspecified	None	None	Trunk	IV
3[b]	Army	Vietnam	None	None	Face/head	II
4[b]	Navy	Persian Gulf War	None	None	Trunk	IV
5[a]	Air Force	Unspecified	HUE	Grandmother	Unknown	IV
6[a]	Army	Unspecified	None	None	Unknown	IV
7[a]	Army	Vietnam	None	None	Face/head	III
8[a]	Navy	Vietnam	None	None	Trunk	IV
9[a]	Army	Vietnam	None	None	Unknown	IV
10[a]	Army	Vietnam	Agent Orange	None	Unknown	IV
11[a]	Air Force	Vietnam	Agent Orange	None	Unknown	IV
12[a]	Air Force	Unspecified	HUE	None	Extremity	IV
13[b]	Navy	Vietnam	Asbestos	None	Unknown	IV
14[b]	Marine Corps	Post-Vietnam	HUE	None	Extremity	III
15[b]	Marine Corps	Vietnam	Agent Orange	Sister	Trunk	IV
16[b]	Navy	Vietnam	Agent Orange	Mother	Trunk	II
17[a]	Air Force	Vietnam	Agent Orange	None	Trunk	III
18[a]	Army	Unspecified	Agent Orange	None	Trunk	I
19[b]	Army	Vietnam	None	None	Face/head	IV
20[a]	Army	Vietnam	None	None	Face/head	IV
21[a]	Army	Vietnam; Korean	HUE	None	Unknown	IV
22[a]	Air Force	Vietnam	None	None	Face/head	III
23[a]	Army	Vietnam	Agent Orange	Mother	Trunk	IV
24[b]	Navy	Persian Gulf War	None	Father	Trunk	III
25[a]	Army	Unspecified	Agent Orange	None	Face/head	IV
26[a]	Army	Vietnam	Agent Orange	None	Unknown	IV
27[a]	Army	Vietnam	None	None	Unknown	IV
28[b]	Army	Vietnam	Agent Orange	None	Unknown	IV
29[a]	Navy	Vietnam	None	None	Trunk	IV
30[b]	Navy	Vietnam	Agent Orange	None	Unknown	III
31[b]	Army	Vietnam	Agent Orange	None	Face/head	III
32[a]	Navy	Post-Vietnam	None	None	Unknown: Ocular	IV
33[a]	Army	Post-Vietnam	None	None	Unknown	IV
34[a]	Marine Corps	Unspecified	None	None	Trunk	III
35[a]	Army	Vietnam	Agent Orange	None	Extremity	IV

Abbreviation: HUE, history of unspecified exposure.
[a]Testing platform: FoundationOne CDx.
[b]Testing platform: Tempus Xt.

TABLE 2. Gene Mutations in the Study Population vs the Top 20 Mutated Genes in Cutaneous Melanoma General Population[a]

	General population[a]			Study population (N = 35)			Agent Orange subgroup (n = 13)		
Gene	Total cases, No.	Mutation cases, No.	Mutation frequency, %	Mutation cases, No.	Mutation frequency, %	*P* value[b]	Mutation cases, No.	Mutation frequency, %	*P* value[c]
TERT promoter[4]	70	50	71	27	77	.56	12	92	.11
CDKN2A[5]	6763	657	10	15	43	< .001	6	46	< .001
BRAF[5]	30,573	12,601	41	13	37	.63	4	31	.46
NF1[5]	4003	791	20	11	31	.11	6	46	.02
TP53[5]	6670	1734	26	9	26	.99	3	23	.81
NRAS[5]	17,436	2714	16	8	23	.26	3	23	.49
PIK3CA[5]	6062	520	9	2	6	.53	0	0	.26
ERBB4[5]	4400	824	19	2	6	.05	1	8	.31
ROS1[5]	3547	880	25	2	6	.01	1	8	.16
NOTCH1[5]	4174	634	15	2	6	.14	1	8	.48
GRIN2A[5]	3566	1012	28	1	3	.001	1	8	.11
KDR[5]	3863	625	16	1	3	.04	0	0	.12
KMT2C (MLL3)[5]	2887	657	23	1	3	.01	0	0	.049
KMT2D (MLL2)[5]	3400	703	20	1	3	.01	0	0	.07
LRP1B[5]	2438	942	39	1	3	< .001	0	0	.004
PTPRT[5]	2621	610	23	1	3	.01	0	0	.049
KIT[5]	9851	814	8	0	0	.08	0	0	.29
HRAS[5]	8576	736	9	0	0	.06	0	0	.26
PTCH1[5]	4428	766	17	1	3	.03	0	0	.10
FAT4[5]	2109	610	29	0	0	< .001	0	0	.02
PREX2[5]	3141	776	25	0	0	< .001	0	0	.04

[a]Based on results from the Cancer Genome Atlas and Catalogue of Somatic Mutations in Cancer.[4,5]
[b]Between the study population and the reference population.
[c]Between the Agent Orange subgroup and the reference population.

The Catalogue of Somatic Mutations in Cancer (COSMIC) was used to identify the most commonly mutated genes in melanomas from The Cancer Genome Atlas for the general population.[4,5] The literature was consulted to determine the MSI status and TMB in melanomas from The Cancer Genome Atlas for separate reference populations.[6,7] The frequency of MSI-high (MSI-H) status, TMB ≥ 10 mutations/megabase (mut/Mb), and mutations in each of the 20 most commonly mutated genes was determined and compared between melanomas from The Cancer Genome Atlas and KCVAMC cases. Corresponding *P* values were calculated to identify significant differences. Values were calculated for the entire sample as well as a subgroup with Agent Orange (AO) exposure. The study was approved by the KCVAMC Institutional Review Board.

RESULTS

The mean (SD) age of study participants was 72.9 (9.4) years (range, 39-90 years). The mean (SD) duration of military service was 1654 (1421) days (about 4 years, 6 months, and 10 days). Of the 35 patients included, 22 (63%) served during the Vietnam era (November 1, 1965, to April 30, 1975) and 2 (6%) served during the Persian Gulf War era (August 2, 1990, to February 28, 1991). Seventeen veterans

(49%) served in the Army, 9 in the Navy (26%), 5 in the Air Force (14%), and 4 in the Marine Corps (11%). Definitive AO exposure was noted in 13 patients (37%) (Table 1).

Of the 35 patients, 24 (69%) had metastatic disease and the primary site of melanoma was unknown in 14 patients (40%). One patient (Patient 32) had an intraocular melanoma. The primary site was the trunk for 11 patients (31%), the face/head for 7 patients (20%) and extremities for 3 patients (9%). Eight patients (23%) were pT3 stage (thickness > 2 mm but < 4 mm), 7 patients (20%) were pT4 stage (thickness > 4 mm), and 5 patients (14%) were pT1 (thickness ≤ 1 mm). One patient had a primary lesion at pT2 stage, and 1 had a Tis stage lesion. Three patients (9%) had a family history of melanoma in a first-degree relative.

The list of genes mutated in melanoma cells in the study population is provided in the eAppendix (available at doi:10.12788/fp.0607).[10,11] Twenty-seven patients (77%) had mutations in *TERT* promoter, 15 (43%) in *CDKN2A/B*, 13 (37%) in *BRAF*, 11 (31%) in *NF1*, 9 (26%) in *TP53*, and 8 (23%) in *NRAS* (Table 2). The majority of mutations in *TERT* promoter were c.-146C>T (18 of 27 patients [67%]), whereas c.-124C>T was the second-most common (8 of 27 patients [30%]). The 2 observed mutations in the 13 patients with *BRAF* mutations were V600E and V600K, with almost equal distribution (54% and 46%, respectively). The mean (SD) TMB was 33.2 (39) mut/Mb (range, 1-203 mut/Mb). Ten patients (29%) had a TMB < 10 mut/Mb, whereas 24 (69%) had a TMB > 10 mut/Mb. The TMB could not be determined in 1 case. The frequency of TMB-high tumors in the study population compared with frequency in the reference population is shown in Table 3.[12] Only 3 patients (0.64%) in the reference population had MSI-H tumors, and the microsatellite status could not be determined in those tumors (Table 4).[13] Table 5 outlines statistically significant findings.

Agent Orange Subgroup

AO was a tactical herbicide used by the US military, named for the orange band around the storage barrels. Possible mutagenic properties of AO have been attributed to its byproduct, dioxin. Among the most common cancers known to be associated with AO exposure are bladder and prostate carcinoma and hematopoietic neoplasms. The association between genetic alterations and AO exposure was studied in veterans with prostate cancer.[14] However, to our knowledge, insufficient information is available to determine whether an association exists between exposure to herbicides used in Vietnam or the contaminant dioxin and melanoma. Because a significant proportion of this study population had a well-documented history of AO exposure (37.1%), we were able to analyze them as a subgroup and to separately compare their mutation frequency with the general population.

Results were notable for different distributions of the most frequently mutated genes in the AO subgroup compared with the whole study population. As such, *TERT* promoter remained the most frequently mutated gene (92%), followed by *CDKN2A/B* (46%); however, frequency of mutations in *NF1* (46%) outnumbered those of *BRAF* (31%), the fourth-most common mutation. Moreover, when compared with the general melanoma population, a significantly higher frequency of mutations in the *NF1* gene was observed in the AO subgroup—not the entire study population.

TABLE 3. Frequency of TMB-High Tumors in Study Population Compared With Reference Population

	Study population (N = 35)	AO subgroup (n = 13)	Reference population (N = 472)
High TMB tumors, No. (%)[a]	24 (69)	9 (69)	233 (49)
Low TMB tumors, No.[b]	10	4	239
P value	.01	.16	

Abbreviations: AO, Agent Orange; TMB, tumor mutational burden.
[a]TMB ≥ 10 mut/Mb.
[b]TMB < 10 mut/Mb.

TABLE 4. Frequency of MSI-H Tumors[7] (*P* = .64)

MSI-H tumors	Study population (N = 35)	Reference population (N = 470)[7]
No.	0	3
Rate, %	0	.64

Abbreviation: MSI-H, microsatellite instability-high.

DISCUSSION

Given that veterans constitute a distinct population, there is reasonable interest in investigating characteristic health issues related to military service. Skin cancer—melanoma in particular—has been researched recently in a veteran population. The differences in demographics, tumor characteristics, and melanoma-specific survival in veterans compared with the general population have already been assessed. According to Chang et al, compared with the general population, veterans are more likely to present with metastatic disease and have lower 5-year survival rates.[8]

TABLE 5. Summary of Statistically Significant Findings

Mutation	General population frequency, %	Study population frequency, %	*P* value[a]	Agent Orange subgroup frequency, %	*P* value[b]
CDKN2A[c]	10	43	< .001	46	< .001
ROS1[d]	25	6	.01	8	.16
GRIN2A[d]	28	3	.001	8	.11
KDR[d]	16	3	.04	0	.12
KMT2Cc (MLL3)	23	3	.01	0	.049
KMT2Dd (MLL2)	20	3	.01	0	.07
LRP1B[c]	39	3	< .001	0	.004
NF1[e]	20	31	.11	46	.02
PTPRT[c]	23	3	.01	0	.049
PTCH1[d]	17	3	.03	0	.10
FAT4[c]	29	0	< .001	0	.02
PREX2[c]	25	0	< .001	0	.04
High tumor mutational burden[d]	49	71	.01	69	.16

[a]Between the study population and the general population.
[b]Between the Agent Orange subgroup and the general population.
[c]Genes whose mutation frequency was significantly different between both veteran populations (whole study and Agent Orange subgroup) and the general population.
[d]Genes whose mutation frequency was significantly different between whole study population (N = 35) and the general population.
[e]Genes whose mutation frequency was significantly different between Agent Orange subgroup (n = 13) and the general population.

Melanoma is one of the most highly mutated malignancies.[15] Fortunately, the most common mutation in melanoma, *BRAF* V600E, is now considered therapeutically targetable. However, there are still many mutations that are less often discussed and not well understood. Regardless of therapeutic implications, all mutations observed in melanoma are worth investigating because a tumor's genomic profile also can provide prognostic and etiologic information. Developing comprehensive descriptions of melanoma mutational profiles in specific populations is critical to advancing etiologic understanding and informing prevention strategies.

Our results demonstrate the high prevalence of *TERT* promoter mutations with characteristic ultraviolet signature (C>T) in the study population. This aligns with general evidence that *TERT* promoter mutations are common in cutaneous melanomas: 77% of this study sample and up to 86% of all mutations are *TERT* promoter mutations, according to Davis et al.[15] *TERT* promoter mutations are positively associated with the initiation, invasion, and metastasis of melanoma. In certain subtypes, there is evidence that the presence of *TERT* promoter mutations is significantly associated with risk for extranodal metastasis and death.[16] The second-most common mutated gene in the veteran study population was *CDKN2A/B* (43%), and the third-most mutated gene was *BRAF* (37%).

In chronically sun-exposed skin *NF1*, *NRAS,* and occasionally *BRAF* V600K mutations tend to predominate. *BRAF* V600E mutations, on the other hand, are rare in these melanomas.[15] In our study population, the most prevalent melanoma site was the trunk (31%), which is considered a location with an intermittent pattern of sun exposure.[17]

This study population also had a higher frequency of *CDKN2A/B* mutations. High frequencies of *CDKN2A/B* mutations have been reported in familial melanomas, but only 1 patient with *CDKN2A/B* mutations had a known family history of melanoma.[15] Tumors in the study population showed significantly lower frequency of mutations in *ROS1*, *GRIN2A*, *KDR*, *KMT2C (MLL3)*, *KMT2D (MLL2)*, *LRP1B*, *PTPRT*, *PTCH1*, *FAT4*, and *PREX2* ($P < .05$).

In this study the subgroup of veterans with AO exposure differed from the whole study pop-

ulation. As such, *CDKN2A/B* mutations were observed with the same frequency as *NF1* mutations (46% each); however, *BRAF* mutations constituted only 31% of the mutations. In addition, the frequency of *NF1* mutations was significantly higher in the AO subgroup compared with the general population, but not in the whole study population.

Our sample also differed from the reference population by showing a significantly higher frequency of TMB-high (ie, ≥ 10 mut/Mb) tumors (71% vs 49%; $P = .01$).[12] Interestingly, no significant difference in the frequency of TMB-high tumors was observed between the AO subgroup and the reference population (69% vs 49%; $P = .16$). There also was no statistically significant difference between the frequency of MSI-H tumors in our study population and the reference population ($P = .64$).[13]

One patient in the study population had uveal melanoma. Mutations encountered in this patient's tumor differed from the general mutational profile of tumors. None of the 21 mutations depicted in Table 2 were present in this sample.[10,11] On the other hand, those mutations frequently observed in intraocular melanomas, *BAP1* and *GNA11*, were present in this patient.[18] Additionally, this particular melanoma possessed mutations in genes *RICTOR*, *RAD21,* and *PIK3R1*.

Limitations

This study population consisted exclusively of male patients, introducing sex as a potential confounder in analyzing differences between the study population and the general population. As noted in a 2020 systematic review, there were no sex-based differences in the frequency of mutations in *BRAF*, *NRAS*, and *KIT* genes.[19] Regarding *NF1* mutations, only *NF1*-mutated acral and mucosal melanomas were more frequently observed in female patients, whereas nonacral *NF1*-mutated melanomas were more frequently observed in male patients.[20] However, there is currently no clear evidence of whether the mutational landscapes of cutaneous melanoma differ by sex.[21] Among the 11 cases with *NF1*-mutatation, site of origin was known in 6, 5 of which originated at nonacral sites. Although the AO subgroup also consisted entirely of male patients, this does not explain the observed increased frequency of *NF1* mutations relative to the general population. No such difference was observed between the whole study population, which also consisted exclusively of male patients, and the general population. The similar frequencies of nonacral location in the whole study population (3 acral, 18 nonacral, 14 unknown site of origin) and AO subgroup (1 acral, 7 nonacral, 5 unknown site of origin) preclude location as an explanation.

The Cancer Genome Atlas Network proposed a framework for genomic classification of melanoma into 4 subtypes based on the pattern of the most prevalent significantly mutated genes: mutant *BRAF*, mutant *RAS*, mutant *NF1*, and triple–wild-type. According to that study, *BRAF* mutations were indeed associated with younger age, in contrast to the *NF1*-mutant genomic subtype, which was more prevalent in older individuals with higher TMB.[22] This emphasizes the need to interpret the potential association of AO exposure and *NF1* mutation in melanoma with caution, although additional studies are required to observe the difference between the veteran population and age-matched general population.

On the other hand, Yu et al reported no significant differences of TMB values between patients aged < 60 and ≥ 60 years with melanoma.[23] In short, the observed differences we report in our limited study warrant additional investigation with larger sample sizes, sex-matched controlling, and age-matched controlling. The study was limited by its small sample size and the single location.

CONCLUSIONS

The genomic profile of melanomas in the veteran population appears to be similar to that of the general population with a few possible differences. Melanomas in the veteran study population showed a higher frequency of *CDKN2A/B* mutations; lower frequency of *ROS1*, *GRIN2A*, *KDR*, *KMT2C (MLL3)*, *KMT2D (MLL2)*, *LRP1B*, *PTPRT*, *PTCH1*, *FAT4,* and *PREX2* mutations; and higher TMB. In addition, melanomas in the AO subgroup showed higher frequencies of *NF1* mutations. The significance of such findings remains to be determined by further investigation.

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Author disclosures

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Ethics and consent

The study was approved by the Kansas City Veterans Affairs Medical Center Institutional Review Board.

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eAPPENDIX. List of Mutated Genes and Specific Mutations With Respective Frequency in the Study Population (N = 35)

Gene	Mutation	Mutation, No. (%)
TERT promoter	c.-146C>T	18 (51)
	c.-124C>T	8 (23)
	139_-138CC>TT	1 (3)
	Total	27 (77)
CDKN2A/B	Loss both	2 (6)
	Copy number loss both	2 (6)
	p.P81L missense LOF 35.7%	1 (3)
	P16INK4a splice site 151-1_151GG>AA and p14ARF splice site 194-1_194GG>AA subclonal	1 (3)
	p16INK4a P70fs*36 and p14ARF Q85fs*62	1 (3)
	p16INK4a F90L and p14ARF P105T	1 (3)
	CDKN2A p.V51I splice region variant LOF 76.3%	1 (3)
	p16INK4a R80* and p14ARF P94L, p16INK4a P81L	1 (3)
	CDKN2A p.A57fs frameshift LOF 33.2%	1 (3)
	CDKN2A p.W110* stop gain LOF 8.7%	1 (3)
	Loss unspecified	1 (3)
	CDKN2A loss	1 (3)
	p16INK4a splice site 151-25_188del63 and p14ARF splice site 194-25_231del63	1 (3)
	Total	15 (43)
BRAF	V600E	7 (20)
	V600K	6 (17)
	Total	13 (37)
NF1	Loss exons 1-7	1 (3)
	p.R1241 stop gain LOF 60.2%	1 (3)
	p.Q1815* stop gain LOF 32.8%	1 (3)
	1527+1_1527+2GT>TC splice site	1 (3)
	p.Q1822* stop gain LOF 49.8%	1 (3)
	Q1395*, Q519* splice site 6007-1G>A	1 (3)
	Q1617*, rearrangement intron 1	1 (3)
	R1204W, W1685*	1 (3)
	p.Q589* stop gain LOF 65.6%	1 (3)
	p.Q1255* stop gain LOF 14.5% p.R2450* stop gain LOF 11.7%	1 (3)
	Q519*, Y2192*	1 (3)
	Total	11 (31)
TP53	p.IR195 stop gain LOF 40.5%	1 (3)
	p.P27L missense LOF 14.9%	1 (3)
	c.559+1G>T splice region variant LOF 38.4%	1 (3)
	p.R110fs frameshift LOF 51.7%	1 (3)
	R213*	1 (3)
	R282W	1 (3)
	p.G187S splice region variant LOF 65.6%	1 (3)
	p.P177S	1 (3)
	Loss unspecified	1 (3)
	Total	9 (26)
NRAS	Q61R	2 (6)
	p.Q61K missense (exon 3) GOF 21.9%	1 (3)
	p.Q61K missense (exon 3) GOF 16.6%	1 (3)
	Q61H	1 (3)
	p.Q61R missense (exon 3) GOF 51.9%	1 (3)
	p.G13D missense (exon 2) GOF 38.2%	1 (3)
	Q61K	1 (3)
	Total	8 (23)
PTEN	V166fs*14	1 (3)
	R130G-subclonal, H196fs*6, G251D	1 (3)
	Loss exons 4-9	1 (3)
	p.V166fs frameshift LOF 8.3%; p.D252G missense LOF 6.1%	1 (3)
	A137fs*42	1 (3)
	Total	5 (14)
SETD2	Q1638*	1 (3)
	Splice site 88-1G>A	1 (3)
	R620*	1 (3)
	R1492*	1 (3)
	Deletion exons 2-3	1 (3)
	Total	5 (14)

ARID2	p.R274*stop gain LOF 7.4% p.R542* stop gain LOF 32.9% p.G1658*stop gain LOF 16.3%; c.1581-1G>A splice region variant LOF 8.8% Total	1 (3) 1 (3) 1 (3) 3 (9)
CBL	Y371N R420Q P417S Total	1 (3) 1 (3) 1 (3) 3 (9)
IDH1	R132C p.R132G missense GOF 15.8% Total	2 (6) 1 (3) 3 (9)
MTAP	Loss unspecified Copy number loss Total	1 (3) 2 (6) 3 (9)
RAC1	P29S unspecified P29S subclonal p.P29S missense GOF 11.5% Total	1 (3) 1 (3) 1 (3) 3 (9)
APC	P1609L Loss exon 16 Total	1 (3) 1 (3) 2 (6)
ATM	P1382fs*6 K468fs*18 Total	1 (3) 1 (3) 2 (6)
CCND1	Amplification Amplification-equivocal Total	1 (3) 1 (3) 2 (6)
DNMT3A	Q696* p.Q656* stop gain LOF 35.8% Total	1 (3) 1 (3) 2 (6)
ERBB4	p.E452K missense GOF 37.7% E452K unspecified Total	1 (3) 1 (3) 2 (6)
FBXW7	L594F S426L, S582L Total	1 (3) 1 (3) 2 (6)
FGF12	E149K Total	1 (3) 1 (3)
FGFR2	R210Q N549K Total	1 (3) 1 (3) 2 (6)
FLT1	R281Q E72K Total	1 (3) 1 (3) 2 (6)
MEN1	R465* p.R98* stop gain LOF 12.8% Total	1 (3) 1 (3) 2 (6)
MSH6	p.F451fs frameshift LOF 49.9% F1104fs*1 Total	1 (3) 1 (3) 2 (6)
MUTYH	G382D p.Y179C missense LOF 48.7% Total	1 (3) 1 (3) 2 (6)
NOTCH1	p.FQ474 stop gain LOF 33.1% E455K Total	1 (3) 1 (3) 2 (6)
NPM1	583-2A>G splice site Loss unspecified Total	1 (3) 1 (3) 2 (6)
PIK3CA	R38H E542K Total	1 (3) 1 (3) 2 (6)

RAD21	Deletion exons 3-4 Amplification Total	1 (3) 1 (3) 2 (6)
RAF1	S257L Amplification Total	1 (3) 1 (3) 2 (6)
ROS1	P1440S E402K subclonal Total	1 (3) 1 (3) 2 (6)
SF3B1	G742D E902K Total	1 (3) 1 (3) 2 (6)
SPEN	S268fs*98 Q1757* Total	1 (3) 1 (3) 2 (6)
ABL1	ABL1-BCR non-canonical fusion	1 (3)
ARID1A	Q1519fs*13	1 (3)
ATRX	Deletion exons 9-10	1 (3)
BAP1	L633fs*4	1 (3)
BRCA2	S2670L	1 (3)
CARD11	D632N	1 (3)
CD70	R163*	1 (3)
CDK6	Amplification-equivocal	1 (3)
CDKN1B	p.Q141* stop gain LOF 11.0%	1 (3)
CHEK2	I157T	1 (3)
CIC	p.Q979 stop gain LOF 38.4%	1 (3)
CREBBP	Q1773*	1 (3)
CRKL	Amplification-equivocal	1 (3)
CTNNB1	S45F	1 (3)
DIS3	p.R780K missense GOF 35.8%	1 (3)
DDR1	R296C	1 (3)
EBF1	p.NQ195 stop gain LOF 17.5%	1 (3)
EGFR	S720F	1 (3)
ERCC3	p.K688K splice region variant LOF 31.5%	1 (3)
FAM46C	p.Q106 stop gain LOF 20.8%	1 (3)
FANCG	Rearrangement intron 13	1 (3)
FGF12	E149K	1 (3)
FGFR1	R445W	1 (3)
FLT3	M664I	1 (3)
GABRA6	W188*	1 (3)
GNA11	Q209L	1 (3)
GNAQ	Q209P	1 (3)
GRIN2A	p.W843* stop gain LOF 18.4%	1 (3)
HGF	E174K	1 (3)

IKZF1	p.Q149* stop gain LOF 29.5%	1 (3)
JAK2	V617F	1 (3)
KDM5C	Q706*	1 (3)
KDR	G494E	1 (3)
KMT2C (MLL3)	p.R2403 stop gain LOF 22.1%	1 (3)
KMT2D (MLL2)	R2734*	1 (3)
KRAS	V14I	1 (3)
LRP1B	c.8663-2A>C splice region LOF 45.9%	1 (3)
MAP2K1 (MEK1)	P124L	1 (3)
MITF	Amplification	1 (3)
MYC	Amplification	1 (3)
PARK2	G354R	1 (3)
PBRM1	p.E967 stop gain LOF 21.9%	1 (3)
PIK3C2G	E425K	1 (3)
PIK3R1	P194fs*12	1 (3)
PMS2	p.Q781 stop gain LOF 20.7%	1 (3)
PPP6C	p.P223S missense LOF 15.2%; p.R301C missense LOF 10.0%	1 (3)
PRKN	p.K427* stop gain LOF 25.2%	1 (3)
PTCH1	Splice site 3306_3306+1GG>AA	1 (3)
PTPRT	c.2370-1G>A splice region variant LOF 28.7%	1 (3)
RAD51D	W268*	1 (3)
RAD54L	E469*	1 (3)
RB1	Splice site 1128-2A>T, C553*	1 (3)
RICTOR	Amplification	1 (3)
RUNX1	c.97+1G>A splice region LOF 13.7%	1 (3)
SLIT2	p.C1385* stop gain LOF 26.4%	1 (3)
SNCAIP	W574*	1 (3)
STK11	L282fs*3	1 (3)
SUZ12	p.K341fs frameshift LOF 11.6%	1 (3)
TBX3	P646S	1 (3)
WT1	M1I	1 (3)

Abbreviations: del, deletion; GOF, gain of function; LOF, loss of function.