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Evaluating the Relationship Between *BRAF* Mutation Class and Patient Demographics in an International Cancer Cohort

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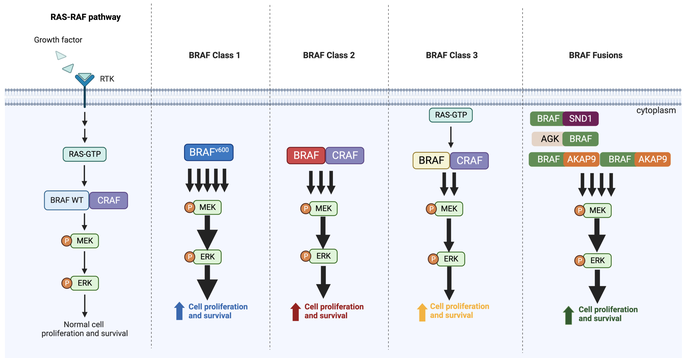
BACKGROUND

BRAF mutations are classified into 4 groups based on distinct molecular characteristics. Targeted therapies for *BRAF* Class 2/3/Fusion are still in development with clinical trials actively enrolling patients, but many barriers to enrollment exist.

Figure 1a: Schematic depicting molecular function of BRAF mutation classes. 1b: BRAF mutations by class



BRAF Class	Protein Change	Occurrence in dataset	BRAF Class	Protein Change	Occurrence in dataset	BRAF Class	Protein Change	Occurrence in dataset	BRAF Class	Protein Change	Occurrence in dataset
1	V600_K601delinsEI	1	2	K601E/I/N/Q	181	2	V504_R506dup	1	Fusion	AGK-BRAF fusion	11
1	V600_K601delinsEN	1	2	L485_A489delinsFS	1	2	V600_K601delinsE	14	Fusion	BRAF-AGK	3
1	V600_S602delinsRKT	1	2	L485_P490delinsF	1	2	V600_R603del	2	Fusion	BRAF-CDK5RAP2 fusion	3
1	V600D/E/G/K/L/R	3355	2	L485F/S/W	16	2	V600_S602del	1	Fusion	BRAF-INTERGENIC	16
2	A598_T599insI	1	2	L505H	2	2	V600_W604delinsDG/GR	5	Fusion	BRAF-KIAA1549	10
2	A598D	1	2	L597P/Q/R/S/V	70	2	X506_X506insRYSG	2	Fusion	BRAF-MKRN1	16
2	A598dup	1	2	M484_L485delinsIM	1	3	D594A/E/G/H/N/V/Y	303	Fusion	BRAF-NDUFB2	3
2	D594_T599dup	23	2	N486_A489delinsK	1	3	E501K/Q/V	15	Fusion	BRAF-SND1	18
2	E586K	13	2	N486_A489delinsR	1	3	F247L	6	Fusion	BRAF-TMPRSS2 fusion	3
2	F468S	8	2	N486_P490del	30	3	G466A/E/L/R/V	174	Fusion	BRAF-TRIM24 fusion	3
2	F595I/L/S	12	2	P367L/S	12	3	G469E	31	Fusion	KIAA1549-BRAF fusion	6
2	G464A/E/I/R/V	48	2	S602_R603dup	1	3	G596C/D/R/S/V	43	Fusion	Other Fusions	126
2	G469A/I/K/L/L/R/S/V	295	2	T599_V600delinsR	1	3	K483E/N/T	13			
2	I592_A598dup	1	2	T599_V600insDT/EIAT/H/Q	5	3	N581D/H/I/S/T/Y	134			
2	K499E	1	2	T599delinsIP	3	3	Q257R	2			
2	K601_S602delinsNT	1	2	T599dup	17	3	S467L	34			
2	K601_S605delinsD	1	2	T599I	5	3	V471F	4			
2	K601_S605delinsN	2	2	V487_P492delinsA	1	Fusion	AGAP3-BRAF fusion	3			

OBJECTIVE

Determine whether *BRAF* mutation class varies according to key demographic differences in populations of cancer patients.

METHODS

Key Inclusion Criteria:

- BRAF mutation on AACR genie database v12

Key Exclusion Criteria:

- VUS (Variant of Uncertain Significance)
- Unclassifiable mutation
- Age < 20
- Incomplete information age or sex

AACR American Association for Cancer Research FINDING CURES TOGETHER

PROJECTGENIE Genomics Evidence Neoplasia Information Exchange

RESULTS

Figure 2: Consort diagram

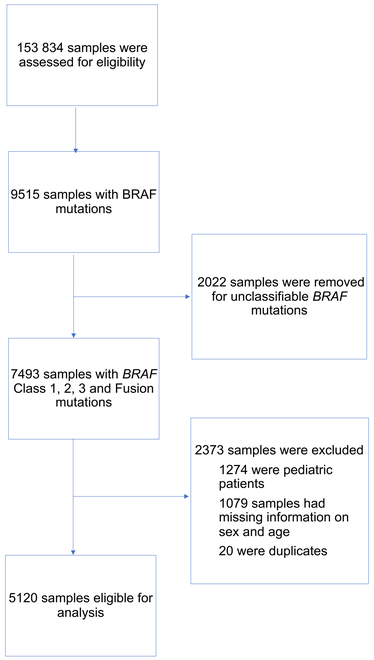


Table 1: Baseline Demographic and Clinical Characteristics of Patients

Characteristics	All patients (n=5120)	Class 1 (n=3358)	Class 2 (n=782)	Class 3 (n=759)	Fusion (n=221)
Age					
Median - yr	62 (20-90)	62 (20-90)	62 (20-90)	62 (22-90)	62 (20-90)
Distribution - no./total no. (%)					
<60 yr	2180 (43)	1532 (46)	241 (31)	291 (38)	116 (52)
≥60 yr	2940 (57)	1826 (54)	541 (69)	468 (62)	105 (48)
Gender - no./total no. (%)					
Male	2537 (50)	1581 (47)	400 (51)	441 (58)	115 (52)
Female	2583 (50)	1777 (53)	382 (49)	318 (42)	106 (48)
Race - no./total no. (%)					
Asian	212 (4)	138 (4)	24 (3)	32 (4)	18 (8)
Black	192 (4)	95 (3)	42 (5)	41 (5)	14 (6)
White	4504 (88)	2977 (89)	691 (88)	659 (87)	177 (80)
Other	212 (4)	148 (4)	25 (3)	27 (4)	12 (5)
Sample type - no./total no. (%)					
Primary site	2421 (47)	1560 (46)	387 (49)	369 (49)	105 (48)
Metastatic	2122 (41)	1379 (41)	332 (42)	304 (40)	107 (48)
Not reported	577 (11)	419 (12)	63 (8)	86 (11)	9 (4)
Type of Tumour - no./total no. (%)					
Melanoma	1591 (31)	1187 (35)	189 (24)	174 (23)	41 (19)
Colorectal Cancer	1061 (21)	842 (25)	67 (9)	136 (18)	16 (7)
Non-Small Cell Lung Cancer	714 (14)	237 (7)	243 (31)	203 (27)	31 (14)
Thyroid cancer	689 (12)	656 (20)	14 (2)	0	19 (9)
Glioma	201 (4)	118 (4)	26 (3)	23 (3)	34 (15)
Unknown primary	125 (2)	56 (2)	25 (3)	38 (5)	6 (3)
Bladder Cancer	39 (1)	3 (0.1)	16 (2)	18 (2)	2 (1)
Hepatobiliary	75 (1)	27 (0.8)	20 (3)	23 (3)	5 (2)
Pancreatic cancer	72 (1)	25 (0.7)	31 (4)	5 (1)	11 (5)
Prostate cancer	72 (1)	1 (0.03)	42 (5)	6 (1)	22 (10)
Other	481 (9)	206 (6)	108 (14)	133 (18)	34 (15)
Co-Mutations - no./total no. (%)					
NF-1	234 (5)	59 (2)	57 (7)	114 (15)	4 (2)
RAS (HRAS, NRAS and/or KRAS)	390 (8)	44 (1)	115 (15)	225 (30)	6 (3)

Figure 3: Distribution of *BRAF* mutations according to Gender

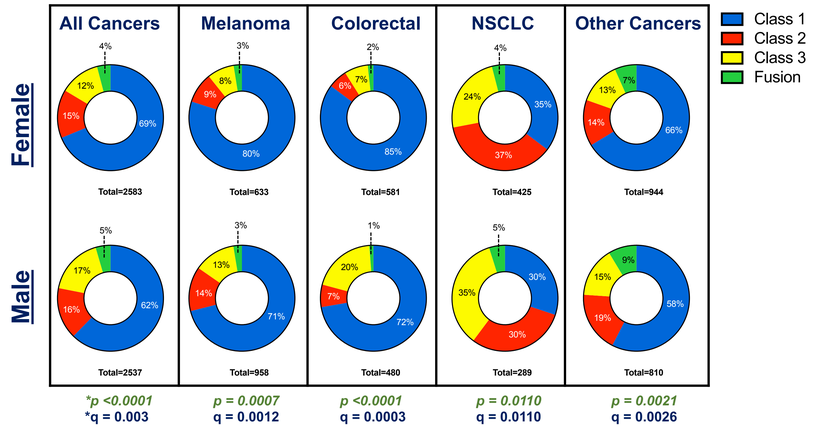
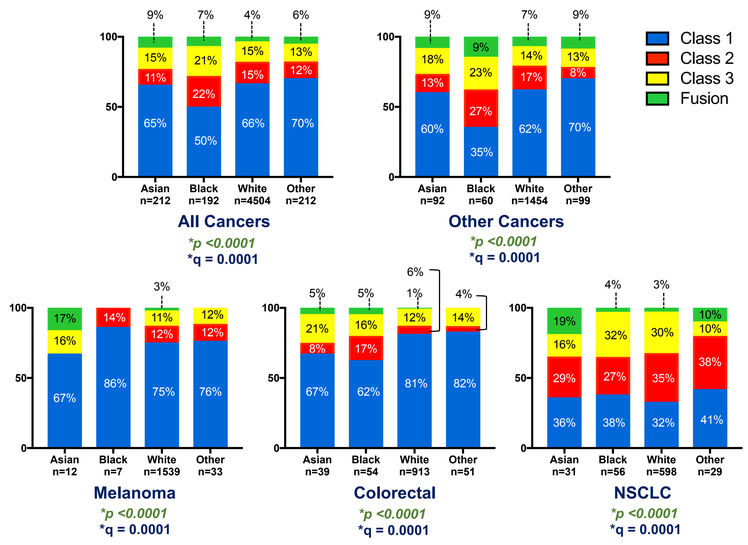


Table 2: Multivariable Analyses of factors associated to non-V600 BRAF mutations (Class 2/3/Fusion) vs. V600 BRAF mutations (Class 1)

	Univariable			Multivariable		
	OR	95% CI	P value	OR	95% CI	P value
Gender						
Male vs Female	1.33	1.19 to 1.50	<0.0001	1.55	1.35 to 1.76	<0.0001
Age						
≥60 vs <60	1.44	1.28 to 1.62	<0.0001	1.28	1.12 to 1.46	<0.0001
Primary Race						
Black vs other	2.00	1.50 to 2.67	<0.0001	1.58	1.13 to 2.20	0.007
Primary tumour type						
Melanoma	0.54	0.48 to 0.62	<0.0001	0.50	0.43 to 0.59	<0.0001
Colorectal	0.42	0.36 to 0.50	<0.0001	0.38	0.31 to 0.46	<0.0001
NSCLC	4.89	4.13 to 5.79	<0.0001	3.08	2.53 to 3.75	<0.0001
Genomic co-mutations						
RAS mt vs wild-type	18.4	13.37 to 25.34	<0.0001	19.18	13.80 to 26.64	<0.0001

Figure 4: Distribution of BRAF mutations according to race and primary cancer type



*Chi-square test was used to evaluate significant differences between groups
*P values corrected by the Benjamini–Hochberg method to determine false discovery rate–corrected Q values, which are considered significant when Q is less than 0.05.

CONCLUSIONS

- Class 3 *BRAF* mutations are more common in men vs. women across all tumor types, contrary to Class 1 *BRAF* mutations which occur more in women.
- Class 2 and 3 *BRAF* mutations are more common in Black patients across all tumor types and in colorectal cancer in particular.
- Asian patients with NSCLC and melanoma have a higher prevalence of *BRAF* fusion mutations.
- More research is needed to determine the molecular mechanisms governing these associations.
- Multiple clinical trials are currently investigating targeted therapy strategies for patients with these atypical but actionable *BRAF* mutations. Our study may help to identify patient populations most likely to benefit from these clinical trials.
- Our results highlight the need to address disparities in access to next generation sequencing and to clinical trial enrollment so that patients with actionable oncogenic Class 2 and 3 *BRAF* mutations can receive novel targeted therapies.

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