Differences in the molecular landscape of cancer between African American (AA) and Caucasian (CC) cancer patients.

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Abstract #6588

Background: The racial and ethnic differences in the molecular pathology of cancer have yet to be fully characterized. Here we report on the molecular landscape of tumors classified by race.

Methods: DNA from formalin-fixed paraffin-embedded samples was sequenced using the Illumina NextSeq (Agilent SureSelect XT, 592 gene selected based on COSMIC database) and MiSeq (TruSeq, 47 gene) to evaluate mutation and gene amplification. Immunohistochemistry (IHC) evaluated protein expression. The exome aggregation consortium database was evaluated for known ethnicity associations.

Results: Tumors from 355 AA and 833 CC patients were included. In both groups, the most prevalent cancer types were NSCLC (AA:19.6%, C:13.4%), CRC (24.2%; 18.7%) and breast cancer (BC; 14.6%, 11%). When only pathogenic or presumed pathogenic mutations (determined according to ACMG guidelines) were considered, in CRC, AA had fewer BRAF mutations than CC (3.5% vs. 10.6%, p = 0.022), including the V600E variant (1.7% AA vs 8.5% CC, p = 0.01). AA had lower ATM mutations vs. CC (1.7 vs. 6.6%, p = 0.0468) but higher MEK1 (2.5% (D67N and K57N) vs. 0, p = 0.035) and PIK3CA mutations (22% vs. 11%, p = 0.01, no difference in distribution of exon 9 /20), KRAS was similar. In NSCLC adenocarcinoma, BRAF mutation was more frequent in AA than CC (14% vs. 4%, p=0.02); in NSCLC squamous cell carcinoma, PD-L1 tumor expression using SP142 (Ventana)was significantly higher in CC than AA (35% vs. 0, p=0.026).In high grade glioma, TP53 (40% vs. 11%, p=0.02) and PTEN mutation rates (33% vs. 0, p=0.005)are significantly higher in CC while MDM2 amplification (40% vs. 3%, p=0.03) and PTPN11 mutation rates (11% vs. 0, p=0.01) are higher in AA patients. In CRC, IHC analysis revealed that AA had higher TOPO2A (95% vs. 84%, p = 0.005) and EGFR (65% vs. 53%, p=0.047)expression than CC. In BC, AA had higher RRM1 (43% vs. 24%, p = 0.01), lower TLE3 (59% vs. 74%, p = 0.02) and lower TS (25% vs. 46%, p = 0.001) expression.

Conclusions: Different molecular landscapes of the most common cancers between AA and CC patients were seen. Observations such as higher BRAF V600E mutation rates in CC CRC may have clinical implications. Further investigation is warranted to explore these differences.

Results

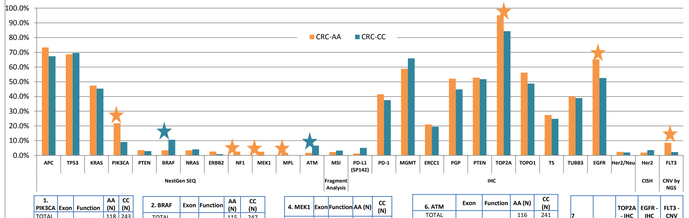
Figure 1: Patient characteristics. Comparison of four tumor types are included in this study. Patient age is not significantly different when tumors from all cancer types are considered. Patient gender is well balanced with the exception of breast cancer.

		CRC (N=459)		NSCLC (N=341)		High Grade Glioma (HGG) (N=107)		Breast Cancer (N=281)		All cancers analyzed (N=1188)	
Ethnicity		AA	CC	AA	CC	AA	CC	AA	CC	AA	CC
Patient Age		61	58	63	66	47	56	55	59	59	60
	Female	65	164	59	129	14	38	83	194	221	525
Gender	Male	71	159	51	102	11	44	1	3	134	308
	Primary	68	145	52	106			37	93	157	344
Primary vs. Mets	Mets	67	168	50	114			47	104	164	386
Ethnicity Make up		136 / 323		110 / 231		25 / 82		84 / 197		355 / 833	

AA CC

Figure 2: Selected molecular alterations in AA and CC CRC patients. A star indicates statistical significance (p<0.05). Tables below provide additional details of significantly differentially altered biomarkers. (1-6: specific protein changes on genes mutated at significantly different rates between the two groups; 7: Frequency and p values for TOP2A, EGFR IHC and FLT3 CNV).

- BRAF mutations are more than three times as prevalent in CC CRC patients than AA, particularly, V600E variant is seen in 8.5% of CC CRC patients but only 1.7% in AA CRC patients, p=0.01.
- PIK3CA mutation is more than twice as prevalent in AA CRC tumors than CC, with exon 9 mutations being more prevalent than exon 20 mutations in both groups.
- ATM mutations, mostly truncating mutations and frameshift mutations occurring at various exons, are significantly higher in CC CRC patients.



1. PIK3CA	Exon	Function	AA (N)	CC (N)
TOTAL			118	243
R88Q	1	P		2
E109del		PP	1	1
N345K	4	PP		3
E542K	9	P	10	6
E545A		P		1
E545G		P	1	
E545K		P	6	4
Q546K		P	1	
Q546R		P		1
Y1021C	20	PP	1	
M1043I		P	1	
G1049R		P	1	1
H1047L		P	2	1
H1047R		P	2	2
P value			<0.001	

2. BRAF	Exon	Function	AA (N)	CC (N)
TOTAL	11		115	247
G464V		P		1
G466V		P		1
D594G		PP	2	
D594N		PP		1
L597V		PP		1
V600_K601d elinsE		PP		1
V600E		P	2	21
P value			0.0224	

3. NF1	Exon	Function	AA (N)	CC (N)
TOTAL			78	169
R440X	12	P	1	
R1769X	38	P	1	
c.6819+1G>A	45	P	1	
P value			0.0366	

4. MEK1	Exon	Function	AA (N)	CC (N)
TOTAL			78	169
D67N	2	PP	1	
K57N	2	PP	1	
P values			0.0366	

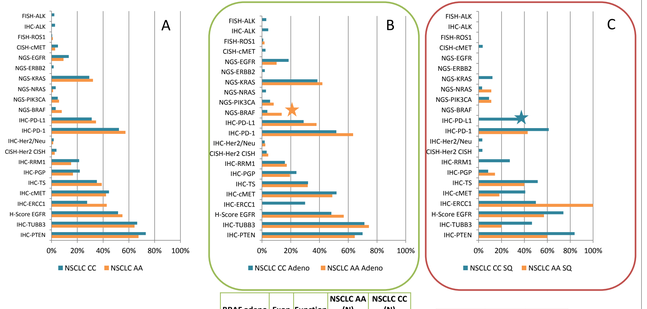
5. MPL	Exon	Function	AA (N)	CC (N)
TOTAL			115	244
Y252H	5	PP	2	
P values			0.0389	

6. ATM	Exon	Function	AA (N)	CC (N)
TOTAL			116	241
S49C	3	PP		4
R337H	8	PP		1
E632K	12	P		1
L1238fs		P		1
Y1241X	25	P		1
L1449X	29	P		1
F1774fs	35	P		1
Q2108X	43	P		1
R2443X	50	P		1
W2638X	53	P	2	
F2799fs	57	P		1
R3008C		P		2
R3008H	63	P		1
P values			0.0468	

7		TOP2A - IHC	EGFR - IHC	FLT3 - CNV
	Pos	99	58	7
	Total	104	89	82
AA	Percent	95%	65%	9%
	Pos	211	102	4
	Total	250	194	176
CC	Percent	84%	53%	2%
P values		0.005	0.0473	0.0404

Figure 3: Selected molecular alternations in AA and CC NSCLC patients. A: Comparison in all NSCLC tumors; B: comparison in adenocarcinoma (N=64 in AA and N=135 in CC); C: Comparison in squamous cell carcinoma (N=14 in AA and N=39 in CC). A star indicates statistical significance (p<0.05).

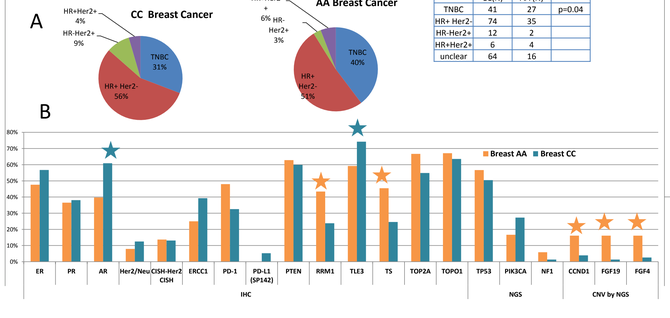
- No significant differences were seen when all AA and CC NSCLC tumors were compared.
- BRAF mutation rate is significantly higher in AA patients with adenocarcinoma compared to CC adenocarcinoma patients. Table shows the specific mutations observed.
- PD-L1 tumor expression using SP142 (Ventana) is significantly higher in CC patients with squamous cell carcinoma and is absent in AA patients.



BRAF adeno	Exon	Function	NSCLC AA (N)	NSCLC CC (N)
Wild type			44	104
G469A	11	P	1	2
D594N	15	PP	2	
G596R	15	P		1
K601E	15	PP	1	
V600E	15	P	3	1
P value			0.0201	

PD-L1 (SP142)	NSCLC AA (N)	NSCLC CC (N)
Positive	0	7
Negative	11	13
P value	0.0257	

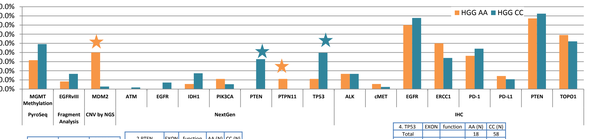
Figure 4: Selected molecular alterations in AA and CC Breast Cancer patients.
A: Distribution of breast cancer subtypes: significantly more TNBC cases are seen in the AA cohort
B: Comparison of biomarkers: 1) Significantly more CC breast tumors express androgen receptor and TLE3 than AA while more AA breast tumors express RRM1 and TS than CC. Comparison in TNBC only (data not shown) generated similar trends for AR, TLE3 and TS, however the difference was not significant. Significance sustains for RRM1 expression in TNBC (69% in AA vs. 20% in CC, p=0.0032).



	CC(N)	AA (N)	
TNBC	41	27	p=0.04
HR+ Her2-	74	35	
HR-Her2+	12	2	
HR+Her2+	6	4	
unclear	64	16	

Figure 5: Selected molecular alterations in AA and CC high grade glioma (HGG) patients. A star indicates statistical significance (p<0.05). Tables below provide additional details of significantly differentially altered biomarkers. (1: Frequency and p value for MDM2 CNV; 2-4: specific protein changes on genes mutated at significantly different rates between the two groups).

- MDM2 gene amplification tested by NextGen is significantly higher in AA HGG tumors compared to CC, and is mutually exclusively of TP53 mutation; TP53 mutation is significantly higher in CC HGG tumors; indicating that p53 inactivation is frequent in both AA and CC HGG, but through distinct mechanisms.
- PTEN mutation rate is significantly higher in CC HGG while PTPN11 mutation rate is significantly higher in AA HGG.



		MDM2-CNV
1		
AA	Pos	2
	Total	5
	Percent	40%
CC	Pos	1
	Total	36
	Percent	3%
P values		0.0348

2.PTEN	EXON	function	AA (N)	CC (N)
Total			18	55
Q17X	1	P		1
T20fs		P		1
G129V	5	PP		1
Q87X		P		1
L103fs		P		1
Q171X		P		1
R173H	6	P		1
Y176fs		P		1
Y180X		P		1
I353fs		P		2
P246L	7	P		1
S249fs		P		1
R335X		P		1
V317fs	8	P		1
Y315X		P		2
P value			0.00517	

3. PTPN11	EXON	function	AA (N)	CC (N)
Total			18	57
G503V	13	PP	2	
T507K	13	PP	1	
P values			0.0108	

4. TP53	EXON	function	AA (N)	CC (N)
Total			18	58
N29fs	3	P		1
H115fs	4	P		1
L130V	5	PP		1
R175H	5	P		2
R181H	5	PP		1
V143A	5	PP		1
H193P	6	PP		1
I195T	6	PP		1
Y205fs	6	P		1
Y220C	6	P		1
G244D	7	PP		1
R248Q	7	P		2
Y236C	7	PP		1
C275S	8	PP	1	
F270L	8	PP	1	
G266E	8	PP		1
P278S	8	PP		1
P301fs	8	P		2
R267W	8	PP		1
R273C	8	P		5
R273H	8	P	1	1
R306X	8	P		1
R337C	10	P		1
R342X	10	P		1
P value			0.02434	

Conclusions

- We compared the molecular profiles between a large cohort of tumors collected from African American and Caucasian patients and analyzed the differences in CRC, NSCLC, Breast cancer and High grade glioma. Key observations included:

1)CRC: significantly higher BRAF V600E mutation rate and ATM mutation rate in CC patients and a significantly higher PIK3CA mutation rate in AA patients.

2)NSCLC: in adenocarcinoma, BRAF mutation rate is significantly higher in AA patients while in squamous cell carcinoma, PD-L1 tumor expression (SP142) is significantly higher in CC patients.

3)Breast cancer: in our cohort, TNBC is more prevalent in AA than CC; RRM1 expression in significantly higher in AA than CC in the complete cohort and in TNBC.

4)High grade glioma: p53 inactivation is frequent in both AA and CC tumors, more frequently by TP53 mutation in CC and by MDM2 amplification in AA.

- Molecular differences observed between AA and CC patients in various cancer types may contribute towards different prognosis and clinical behavior and warrants further investigation. It provides valuable information for prospective trials in personalized medicine.

References

1. Bollig-Fischer, A., A. Bepler, et.al.(2015) “Racial diversity of actionable mutations in non-small cell lung cancer. “ J Thorac Oncol, 10(2): 250-5