Presentation #2206

Racial Diversity and Co-Mutational Analysis of Biologically Relevant Alterations in EGFR Mutant Lung Cancers

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INTRODUCTION

- *EGFR* alterations have important therapeutic implications in lung cancer (LCa).
- The incidence of these alterations, their subtypes, and co-mutational status is well described in Caucasian and East Asian but not African American populations.
- Using the Tempus database, we analyzed real-world data from *EGFR* mutant LCas across races, assessing alteration subtypes and co-mutational profiles.

METHODS

- De-identified records with primary LCa diagnosis tested via Tempus xT assay and had ≥1 pathogenic *EGFR* mutation (SNVs, CNAs, or fusions) were identified.
- Race was determined based on recorded clinical records, and stratified as Caucasian (CA), African American (AA), Asian Pacific Islander (API), unknown or other.
- Somatic pathogenic co-mutations were restricted to genes >5% frequency ≥1 race. Data is described using N(%) or median and IQR. Comparisons were made by Chi-squared/Fisher's Exact or Kruskal-Wallis tests.
- Bonferroni or FDR corrections were applied to pairwise comparisons.

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SUMMARY

• *EGFR* alterations are not uniform across races with a subset seen at an increased frequency in certain racial groups
• L858R mutations were significantly higher in CA versus AA and API versus CA
• EGFR CNVs differed across races as well with increased frequency in AA over CA
• Neither PD-L1 positivity (*p=0.3*) nor median TMB (*p=0.04*) differed across race
• Co-mutations such as *KMT2C* and *GLI1* occurred more frequently in AA as compared to CA and API, which may have therapeutic implications as *KMT2C* is linked to higher TMB and better immunotherapy response, while *GLI1* is involved in resistance to erlotinib
• Understanding these variations in alterations among racial groups can help us develop a more customized approach to patient care

RESULTS

Table 1. Demographic and clinical characteristics at time of biopsy

	CA[1] N = 854	AA[1] N = 103	API[1] N = 174	Other N = 78	Unknown N = 660	p-value[2]
Age at Diagnosis	68	65	66	65	67	0.065
Unknown	11	2	2	0	9	
Gender						0.4
Female	537 (63%)	60 (58%)	120 (69%)	51 (65%)	408 (62%)	
Male	317 (37%)	43 (42%)	54 (31%)	27 (35%)	252 (38%)	
Smoking Status						<0.001
Current/former smoker	467 (59%)	71 (73%)	40 (26%)	38 (51%)	278 (52%)	
Never smoker	325 (41%)	26 (27%)	113 (74%)	37 (49%)	261 (48%)	
Unknown	62	6	21	3	121	
Stage						
Stage 1	61 (11%)	9 (13%)	3 (3.0%)	5 (9.8%)	47 (11%)	
Stage 2	39 (7.0%)	5 (7.2%)	6 (5.9%)	5 (9.8%)	28 (6.8%)	
Stage 3	79 (14%)	8 (12%)	11 (11%)	7 (14%)	50 (12%)	
Stage 4	381 (68%)	47 (68%)	81 (80%)	34 (67%)	287 (70%)	
Unknown	294	34	73	27	248	
Histology						0.008
Adenocarcinoma	652 (78%)	75 (74%)	149 (87%)	68 (88%)	529 (82%)	
Other	187 (22%)	26 (26%)	23 (13%)	9 (12%)	120 (18%)	
Unknown	15	2	2	1	11	
Assay match type						0.062
Tumor only	498 (58%)	48 (47%)	105 (60%)	48 (62%)	407 (62%)	
Tumor-normal matched	356 (42%)	55 (53%)	69 (40%)	30 (38%)	253 (38%)	

[1] CA=Caucasian, AA=Black/African American, API=Asian/Pacific Islander

[2] Kruskal-Wallis rank sum test; Pearson's Chi-squared test

Table 2. Frequency of *EGFR* alteration types

	CA N = 854	AA N = 103	API N = 174	Other N = 78	Unknown N = 660	p-value[1]
Exon 19 deletion	307 (36%)	40 (39%)	73 (42%)	41 (53%)	276 (42%)	0.017
L858R	251 (29%)	17 (17%)	73 (42%)	16 (21%)	185 (28%)	<0.001
T790M	29 (3.4%)	3 (2.9%)	5 (2.9%)	3 (3.8%)	22 (3.3%)	>0.9
Exon 20 insertion	55 (6.4%)	9 (8.7%)	12 (6.9%)	7 (9.0%)	31 (4.7%)	0.2
Other EGFR mutation	133 (16%)	16 (16%)	28 (16%)	13 (17%)	111 (17%)	>0.9
Copy number variant	208 (24%)	34 (33%)	22 (13%)	13 (17%)	139 (21%)	<0.001
Fusion	14 (1.6%)	2 (1.9%)	0 (0%)	0 (0%)	14 (2.1%)	0.2

[1] Pearson's Chi-squared test; Fisher's exact test

Frequency of EGFR Exon 19 and L858R differed among racial groups

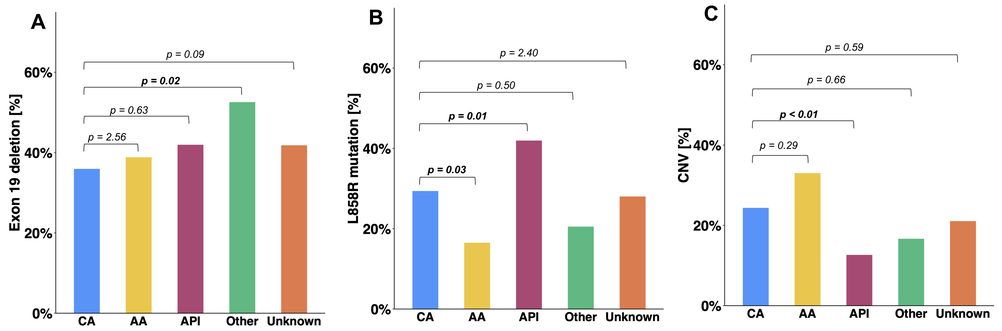

Figure 1. Frequency of pathogenic *EGFR* (A) exon 19 deletion, (B) L858R, and (C) CNVs. Pairwise comparisons were made using chi-squared test between racial groups, with CA patients as the reference group. P-values were corrected for multiple testing using Bonferroni method.

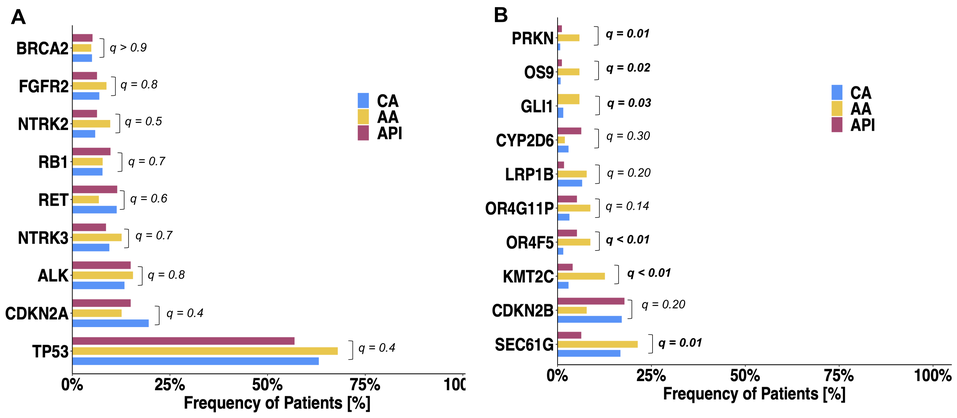

Figure 2. Somatic co-mutations (short variants and copy number aberrations) occurring in 5% or more of known self-reported race populations. Q-values are adjusted for multiple testing using FDR method. (A) Frequency of clinically relevant co-mutated genes. (B)Frequency of co-mutations in genes with greatest differences between race.

Study Limitations

This study was limited to patients who received xT tissue-based testing. This included many advanced stage (III/IV patients. In addition, race was extracted from clinical records (e.g., order forms, patient records, etc.), with a large proportion of patients of unknown race (~35%). Assessing somatic mutational differences across race may yield similar or different conclusions when race/ethnicity is imputed versus self-reported.