RESEARCH

Racial disparities in the genetic landscape of lung cancer

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ABSTRACT

Lung cancer has the highest cancer-related mortality worldwide and in the United States. Although reduced tobacco consumption and advancement in therapies have led to a modest decline in lung cancer death rates over the past two decades; the overall survival rate is still disappointing. Moreover, race-associated disparities are also observed, especially in the clinical outcomes. Socioeconomic factors are considered major contributors in cancer health disparities, however, the differences in the genetic landscape of lung cancer among different racial groups have also been reported. In this review, we shed light on the genetic heterogeneity of lung cancer and race-associated differences in genetic alterations to build a framework for future studies to understand the biological basis of lung cancer disparities.

KEYWORDS: lung cancer, smoking, racial disparity, gene mutation, mitochondria.

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Introduction

Lung cancer (LC) is a lethal disease that took 1.8 million lives globally in 2020 [1]. This year, it is expected to kill nearly 131,880 people in the United States alone, with around 235,760 new diagnoses [1]. Although with advances in therapy, the LC mortality rate has been on a mild decline over the past two decades, the overall 5-year survival rate of LC patients is still at 21.7% [1,2]. Another upsetting fact is that in the United States, LC disproportionately affects people of African descend (AA, African American) compared to those of European origin (CA, Caucasian American). The incidence of LC is 1.15 times higher among the AA men compared to the CA men (85.4/100,000-AA vs. 74.3/100,000-CA), whereas it is 0.86 times lower among the AA women compared to the CA women (49.2/100,000-AA vs. 57.4/100,000-CA) [3]. Similarly, the LC mortality is 1.18 times higher among the AA men than the CA men (63.9/100,000-AA vs. 54.1/100,000-CA) and 0.88 times lower among the AA women than CA women (33.9/100,000-AA vs. 37.9/100,000-CA). Moreover, AA LC patients are 16% less likely to have an early diagnosis and are diagnosed at advanced stages [3]. The 5-year overall survival rate among the AA is also lower (16%) than that of the CA group (19%) [3], underscoring the need to define the factors underlying these racial health disparities.

Potential contributing factors associated with lung cancer disparity

Cigarette smoking plays a significant role in lung tumorigenesis [4–7]. Although the overall cigarette smoking prevalence is similar in both AA and CA populations (15%-AA vs. 16% CA), it appears to be higher among CA women compared to the AA women (15% vs. 12%) [2]. Notably, the metabolic capability of cigarette smoke-derived carcinogens may also vary in different racial populations giving rise to an increased risk of LC. For example, the clearance of cigarette smoke-derived nicotine in the body is regulated by the *CYP2A6* gene, which converts nicotine to cotinine [8]. Different genetic variants of CYP2A6 could potentially be associated with increased risk of LC in AA, as a higher level of cotinine was detected in the blood of AA LC patients compared to CA LC patients. However, a clear link associating the metabolism of nicotine and other tobacco carcinogens with LC disparity has not yet been established. The geographical location and socioeconomic status (SES) of the patients also seem to be important contributing factors in LC health disparities. People from various races living in heavily industrialized areas and areas with a high rate of air pollution may be associated with an increased risk of LC development [9]. In addition, body mass index, alcohol consumption, radon, and alternative or unidentified environmental exposures may also potentially contribute to LC health disparities [10]. On the other hand, the LC risk may increase in socioeconomically disadvantaged racial groups continuously exposed to low SES-derived stressors accompanied by a high prevalence of smoking and other unhealthy behavior.

Genetic heterogeneity in lung cancer and its association with racial health disparity

Through comprehensive next-generation deep sequencing, numerous genetic anomalies have been cataloged in LC. To date, a panel of twenty genes with the highest frequency of mutations have been identified in LC (**Figure 1**). In addition, several different types of genetic mutations have been reported, including nonsense substitution, missense substitution, synonymous substitution, inframe insertion, frameshift insertion or deletion mutations (**Figure 2**). Among these genes, *EGFR* and *KRAS* appear to be the most frequently mutated ones in LC. *EGFR* gene mutations predominantly occur

among non-smoker patients with adenocarcinoma histology, whereas *KRAS* mutations are common among smokers with squamous cell carcinoma histology [11]. In an earlier study by Liedner et al., AA LC patients were found to harbor a significantly lower number of *EGFR* mutations compared to their CA counterparts, thereby predicting a poorer therapeutic response from treatment with the tyrosine kinase inhibitors [12]. A subsequent study by Harada et el. reported a novel *EGFR* exon-20 mutation in AA subjects [13]. In addition, they also identified five *EGFR*-activating mutations in eight AA cases who were either never or light smokes, whereas no *EGFR* mutation was detected among the heavy smokers. Interestingly, a couple of insertional EGFR gene mutations encompassing exon 20 such as N771GY and A767-V769dup were identified exclusively in the AA LC patients . Other than *EGFR*, N375S-MET gene mutation was detected in around 13% of East Asian LC patients and 2.6% CA LC patients but not in the AA LC patients [14]. Inactivation of STK11 gene, also known as *LKB1*, either due to deletion or insertions, have been reported to be more frequent in Caucasian Americans compared to African American and Asian NSLC patients [15,16]. A more recent study by Lusk et al. sequenced 193 AA LC cases for determining the mutational landscape and identified a panel of 88 distinctly mutated genes in addition to the commonly found LC-associated driver mutations [17]. Novel mutations in *PABPC1, PMS2, CDC27, OXCT2, GSTM1, RHPN2, ZC3HC1 and MLL3* genes were noted exclusively in the AA subjects.

Figure 1. The landscape of gene mutations in lung cancer. Top 20 gene mutations identified in lung cancer patients. Data assembled with permission from the COSMIC database (https://cancer.sanger.ac.uk/cosmic). Asterisks indicate the genes, the mutation spectrum of which have been examined in various racial population.

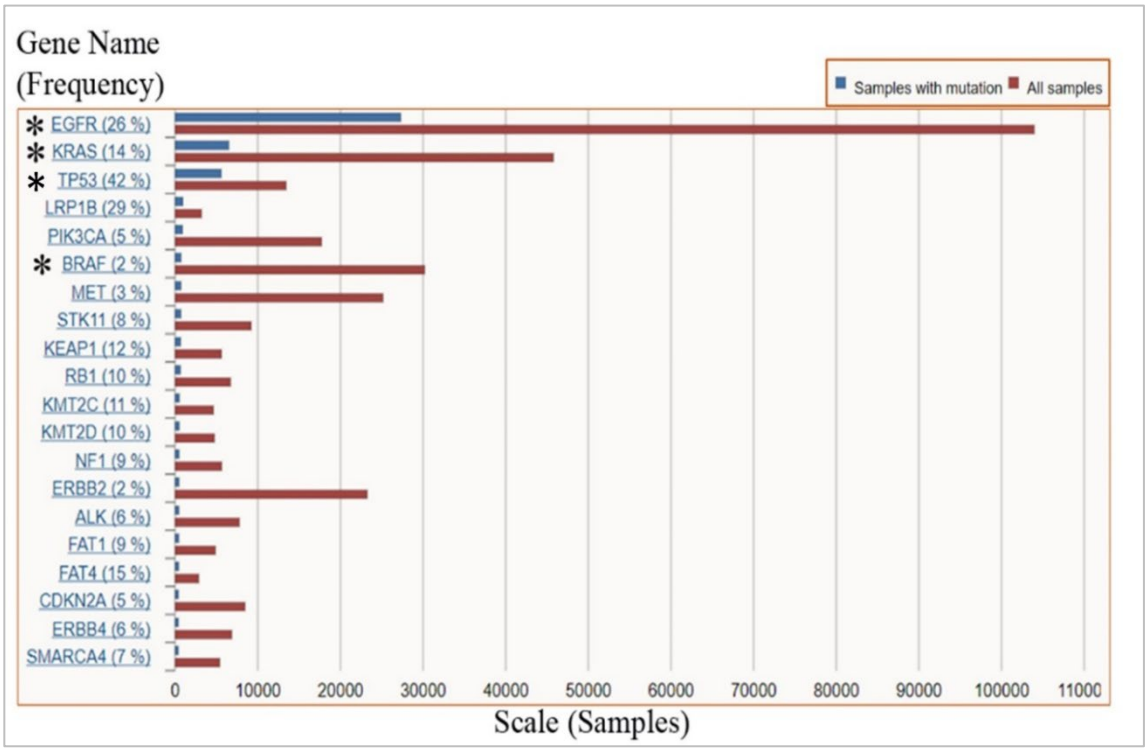
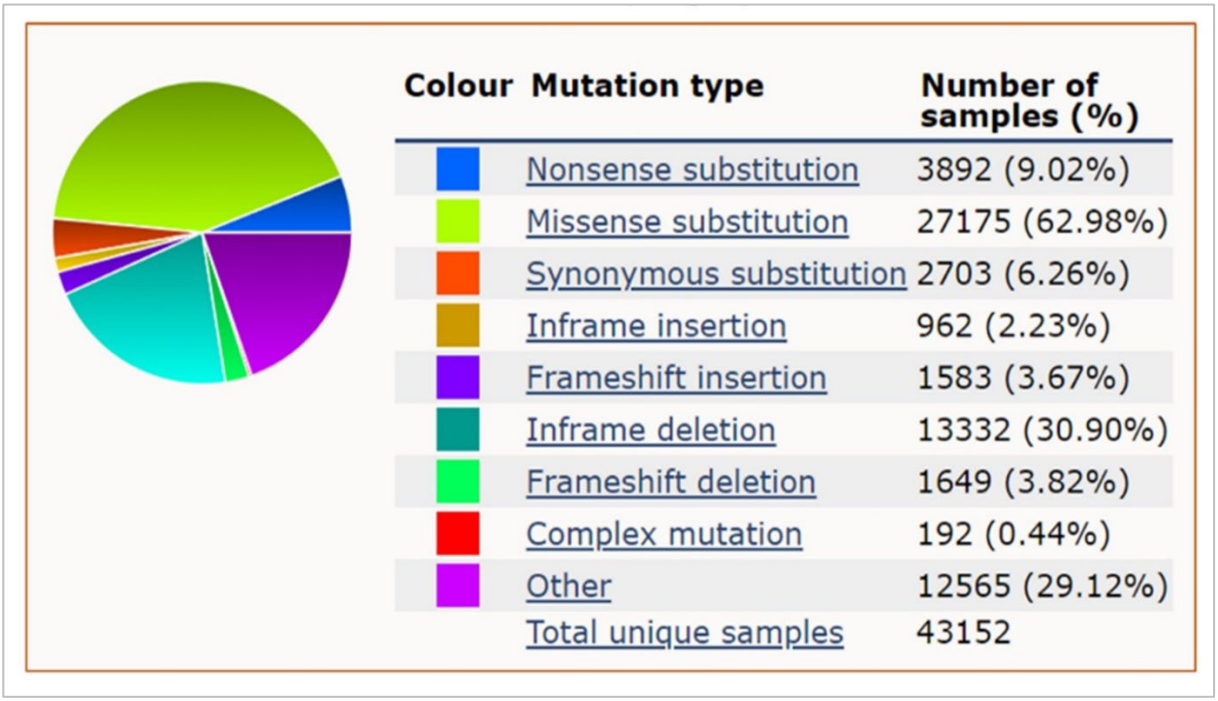


Figure 2. Nature of somatic gene mutation observed in a large number of lung cancer sample pools as analyzed from the COSMIC database (https://cancer.sanger.ac.uk/cosmic).



Colour	Mutation type	Number of samples (%)
	Nonsense substitution	3892 (9.02%)
	Missense substitution	27175 (62.98%)
	Synonymous substitution	2703 (6.26%)
	Inframe insertion	962 (2.23%)
	Frameshift insertion	1583 (3.67%)
	Inframe deletion	13332 (30.90%)
	Frameshift deletion	1649 (3.82%)
	Complex mutation	192 (0.44%)
	Other	12565 (29.12%)
	Total unique samples	43152

In a recent meta-analysis involving a total of 11,867 AA, CA, Hispanic/Latina (HIS) and Asian patients, Costa et al. performed a comparative analysis of LC associated mutations in key genes, including *EGFR*, *ALK*, *ROS-1* and *BRAF* [18]. The most frequently occurring mutations in the AA subjects involved *EGFR* (6%), *BRAF* (1%), *and ALK* (1%). However, the incidence of *EGFR* and *BRAF* mutations was lower in the AA subjects compared to the CA subjects. Another study in 116 LC cases by Hunt et al. reported a higher prevalence of *KRAS* mutations in the AA LC subjects compared to the CA LC subjects [19]. On the contrary, analyses of 121 LC cases by Reinersman *et al.* reported a higher abundance of *KRAS* mutations among the CA LC subjects, compared to the AA LC subjects (26% vs. 17%). Of note, this study also reported higher rate of *EGFR* gene mutations in the AA LC compared to the CA LC subjects (19% vs. 13%) [20]. More information about genetic mutations between CA and AA lung cancer patients is provided in Table 1.

The TP53 gene is well regarded as the key regulator of genomic stability and the most frequently altered molecule in human cancers [21]. In a comprehensive analysis of 431 subjects, kytola et al. have reported a significantly higher frequency of P53 gene mutation in AA LC patients compared to the CA LC patients [22]. Moreover, significantly higher level of amplification of a 5-gene signature, including *MCL1*, *RUNX1T1*, *CDK8*, *CAT6A*, and *RAD21*, was noted in the AA LC cases, compared to the CA LC subjects. In another study, Mitchell et al. reported a higher frequency of mutations in *PTPRT* and *JAK2* in AAs than CAs [23]. They detected *PTPRT* and *JAK2* gene mutations in 24% (13/54) and 7.4% (4/54) AA LC cases, respectively, compared to 8% (30/381) and 2% (7/381) in CAs, respectively. Changes in copy number have also been examined in LC using high-resolution single-nucleotide polymorphism arrays to decipher molecular alterations accumulated during lung tumorigenesis. Considerably higher frequency of copy number gain on 16p13.13 and 16p13.11 was

noted among the East Asian LC patients [14]. On the contrary, genomic loss in 19p13.3 and 19p13.11 regions was noted to be higher in CA LC patients.

Besides lung cancer, race-specific genetic heterogeneity is noted in other human malignanies as well. Mutation frequency was found to be appreciably different in AA and CA colorectal cancer patients for *KRAS* (AA:23-44%; CA:15-45%) and *BRAF* (AA:4-6%; CA:7-14%). Similarly, mutation frequency of *BRAF* was 75-80% in CA papillary thyroid carcinoma patients as compared to 48% in AA patients. In melanoma, mutation frequency of *BRAF* was 8% in AA relative to 21% in CA patients. Such striking differences are also noted for *P53* in breast cancer patients with 43% mutation rate in AA compared to 26.7% in CA women [24].

Table 1. The spectrum of genetic mutations in Caucasian and African American lung cancer patients.

Gene name	Variant	Frequency in patients		Reference
		Caucasian	African American	
		(n^1=102)	(n=53)	[12]
EGFR	G2303A or S768N	17%	2%	
KRAS	Codons 12 and 13 of exon 12	21%	23%	
		(n=264)	(n=245)	[25]
EGFR	-	5.68%	4.89%	
KRAS	-	13.87%	12.87%	
BRAF	-	3.03%	2.44%	
PIK3CA	-	0.75%	0.81%	
EGFRKRAS	Exon 19 deletions and T2573G or L858R c.34G, c.35G and c.38G in codons 12 and 13 of *KRAS*	(n=399) 13.7% 25%	(n=67) 4.8% 30.6%	[26]
		(n=335)	(n=137)	[27]
EGFR	Exon 19 deletions	2%	7%	
		(n=108)	(n=51)	[28]
BRAF	Point mutations in exon 11 or exon 15	13.72%	3.7%	
		(n=9507)	(n=3363)	[18]
EGFR	Activating mutations	12%	6%	
BRAF	-	3%	1%	
ROS-1	-	1%	0%	
ALK	-	2%	1%	
		(n=476)	(n=121)	[20]
EGFR	Exon 19 deletions and Exon 21 (L858R)	13%	19%	
KRAS	Mutation in codon 12 and 13	26%	17%	
		(n=51)	(n=60)	[19]
KRAS	G→T transversion in codon 12	20%	37%	
		(n=381)	(n=52)	[23]

TP53	-	49%	65%	
STK11	-	13%	21%	
RB1	-	4%	13%	
KRAS	-	29%	27%	
EGFR	-	13%	1%	
SMAD4	-	4%	8%	
PIK3CA	-	5%	8%	

[1]Number of patients.

In addition to the nuclear genetic alterations, changes in the mitochondrial genome and dysregulation of various mitochondrial functions also play a pivotal role in human tumorigenesis [29–32]. Mitochondria are regarded as the powerhouse of the cells and generate cellular energy in the form of ATP [33]. In humans, mitochondria are maternally inherited and harbor their own DNA (mtDNA). The human mtDNA is a 16.5-kb double-stranded closed circular molecule having 37 genes, which encode for 12S and 16S rRNAs, 22 tRNAs, and 13 respiratory complex proteins (I, III, IV, and V) essential for the oxidative phosphorylation system (OXPHOS) function [33–36]. Because of the high copy number, mtDNA mutation detection is easier in cells compared to nuclear DNA. Only a handful number of studies have reported mtDNA mutations in LC, including our laboratory [37,38]. The frequency of mtDNA mutations and copy number is higher in Asian patients than in CA patients and associated with EGFR gene mutation [38]. Another study also reported alterations in mtDNA copy number in lung cancer [39], however, a comparative analysis of mtDNA copy number in CA LC and AA LC patients, particularly linking smoking habits remain to be determined. Moreover, the disparities in the alteration in the nuclear genes associated with OXPHOS function are also less well defined between AA LC and CA LC subjects. In an interesting recent study, which utilized TCGA datasets, nuclear DNA encoded mitochondrial OXPHOS pathway-associated genes were found to be upregulated in both lung adenocarcinoma and squamous cell carcinoma of AA patients compared to the subjects of European origin [40]. This study also identified a predominance of ERR1-PGC1α–mediated transcriptional program enrichment, a key regulator of mitochondrial biogenesis in the AA LC subjects compared to the European American subjects. In addition to energy generation, mitochondria are involved in various critical cellular functions, including apoptosis, inflammation, innate and adaptive immune system, T cell function, macrophage polarization, mitophagy, calcium, and damage-associated molecular pattern (DAMP) signaling [29]. As a reason, alterations in mitochondrial metabolism and functions are regarded as cancer hallmarks. However, the differential molecular alteration pattern of these critical pathways remains to be determined in LC patients with different racial backgrounds.

Conclusion and future perspective

Although genetic differences have been reported among racially disparate populations, they have not been mechanistically linked to the observed disproportionate outcomes. With the power of next-generation deep sequencing of thousands of tissue samples, critical molecular pathways associated with lung cancer pathogenesis have been identified, and based on that knowledge, several new lines of targeted therapeutics are in place, and many are currently under clinical trials. Of note, these cataloged molecular changes can also be helpful to develop race-specific biomarkers for diagnosis, prognosis, and therapeutic guidance.

However, the alteration pattern of the majority of these molecules remains largely unknown in racially disparate populations. Moreover, there are some discrepancies in the outcome of the mutational frequency of crucial lung cancer-associated genes among various racial groups in some studies, which could be due to significant differences in sample size, methods used, and/or the specificity of the type of mutations analyzed. Notably, an in-depth analysis of a panel of potential molecular targets other than *EGFR* and *KRAS*, remains to be carried out in diverse racial populations. Moreover, in addition to the mutational landscape, analysis of genome-wide polymorphisms and profiling of genes that are differentially amplified or lost during lung tumorigenesis in various racial groups will also help further our understanding of the genetic basis of lung cancer health disparity. On the other hand, despite increasing and emerging evidence of alterations in mitochondrial DNA and nuclear genes targeting mitochondrial pathways in various human malignancies, their association with lung cancer health disparity has remained largely undefined. In the coming decades, with the advent and power of multi-omics technology, including single-cell genomics and proteogenomics, we hope to achieve appreciable success in characterizing the specific factors and molecular pathways contributing to the lung health disparity to ultimately reduce the disparity gaps.

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Conflict of interest

The authors declare that they have no conflicts of interests.

Authors' Contribution

Study design and oversight: SD, Data acquisition: SD, SA, KSV, APS, SS, Writing and Review: SD, SA, KSV, APS, SS.

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