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99P Landscape of homologous recombination repair gene mutations in different molecular subtypes of NSCLC

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BACKGROUND

Breast cancer Lung cancer is one of the malignant tumors with high morbidity and mortality in the world. PARP inhibitors have become a new line of cancer therapy The mechanism and efficacy of PARP inhibitors have been well studied in some cancers, especially homologous recombination (HR)-deficient ovarian cancer, and several cell line experiments have shown that HR-deficient lung cancers are sensitive to PARP inhibitor. Meanwhile, HHR gene is a potential biomarker for immunotherapy. Herein, we evaluated the characteristics of HRR related gene mutations in Chinese patients with lung adenocarcinoma (LUAD) or lung squamous cell carcinoma (LUSC).

RESULTS

666 of 746 patients were LUAD and 82 patients were LUSC. The proportions of HRR gene mutations in LUAD was 32.28% (215/666) and in LUSC was 41.5% (34/82). The top 5 mutated HRR genes and their incidence are different in LUAD and LUSC (Table 1). Interestingly, BRCA1 gene mutation was not found in LUSC. There was a significant difference in the frequency of five HRR genes between LUAD and LUSC, including BRCA2 (P=0.00034), CHEK2 (P=0.03521), FANCG (P=0.0009), BLM (P=0.02572), FAM175A (P=0.03012) (Table 2). The proportion of tumor mutational burden-high (TMB-H) (≥10 mut/Mb) was significantly higher in HRR mutant than HRR wild-type LUAD or LUSC (LUAD: 36.84% vs 8.82%, P<0.0001, LUSC: 75.86% vs 32.08%, P<0.0001).

METHODS

Tumor specimens from 748 NSCLC patients were analyzed by DNA based NGS with a 1021 gene panel in this study. We analyzed 36 HRR genes, including CHEK1/2, BRCA1/2, BRIP1, CDK12, ATM/ATR, FANCA/C/D2/E/F/G/L/M, MRE11A, NBN, RAD50/51/52, RAD51B/C/D et al.

LUAD			LUSC		
Geen	Number of samples	Frequency (%)	Geen	Number of samples	Frequency (%)
TAM	35	5.26	BRCA2	10	12.20
FANCM	33	4.95	ATR	6	7.32
CDK12	21	3.15	FANCM	6	7.32
BRCA2	21	3.15	FANCA	5	6.10
ATR	18	2.70	CDK12	5	6.10

Table 1. The top 5 mutated HRR genes in LUAD and LUSC

Geen	LUAD		LUSC		P-values
	Number of samples	Frequency (%)	Number of samples	Frequency (%)	
BRCA2	21	3.15	10	12.20	0.00034
CHEK2	4	0.60	3	3.66	0.03521
FANCG	3	0.45	4	4.88	0.0009
BLM	7	1.05	4	4.88	0.02572
FAM175A	1	0.15	2	2.44	0.03012

Table 2. Five significantly different HRR genes between LUAD and LUSC

CONCLUSIONS

In terms of HRR gene mutations, we report that LUAD and LUSC have different mutation landscape. Mutations in HRR genes may serve as a biomarker for PARP inhibitors or ICIs in LUAD and LUSC, which also needs more trials to verify.