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Impact of genetic variant of *HIPK2* on the risk of severe radiation pneumonitis in lung cancer patients treated with radiation therapy

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Abstract

Background: Homeodomain-interacting protein kinase 2 (*HIPK2*) has increasingly drawn attention as recent researches demonstrated its unique role in the regulation of multiple fundamental processes such as apoptosis, proliferation and DNA damage repair. Most importantly, *HIPK2* was shown to play regulatory role in inflammation and influence the phenotype and activity of fibroblasts. In this study, we aimed to evaluate the impact of *HIPK2* gene variant on risk of radiation pneumonitis for patients with pulmonary malignancies.

Methods: 169 lung cancer patients with radiotherapy were included in our prospective study and genotyped by Sanger Sequence method. Multivariable Cox hazard analysis and multiple testing were applied to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of all factors possibly related to the risk of radiation pneumonitis (RP).

Results: Patients with Mean Lung Dose (MLD) ≥ 15 Gy, Lung $V_{20} \geq 24\%$ had higher risk of RP \geq grade 2 compared with those counterparts (HR = 1.888, 95% CI: 1.186–3.004, $P = 0.007$; HR = 2.126, 95% CI: 1.338–3.378, $P = 0.001$, respectively). Importantly, CC genotype of *HIPK2*: rs2030712 were strongly related to an increased occurrence of RP \geq grade 2 (HR = 2.146, 95% CI: 1.215–3.791, $P = 0.009$).

Conclusion: *HIPK2*: rs2030712 was found to be significantly related to RP of grade ≥ 2 in our cohort, and may thus be one of the important predictors of severe RP before radiotherapy, if further validated in larger population.

Trial registration: Our study was prospective and observational. The research was registered in ClinicalTrials.gov database as [NCT02490319](https://clinicaltrials.gov/ct2/show/study/NCT02490319).

Keywords: Radiation pneumonitis, Lung cancer, *HIPK2*, SNP

Background

Globally, lung cancer currently remains as the top one cause of cancer-related mortality. According to the latest statistical report, there are 2.1 million new lung cancer cases and 1.8 million deaths predicted globally in 2018, nearly close to 1 in 5 (18.4%) of all cancer deaths [1]. Among all countries worldwide, China suffered from high rates of male lung cancer (above 40 per 100,000) in 2018. Radiotherapy (RT), with or without chemotherapy,

still acts as the fundamental treatment for lung cancer patients. However, the efficacy of radiotherapy is restrained due to a series of RT-related complications that cause patients intolerance.

Radiation pneumonitis (RP) is a type of inflammation and subsequent fibrosis that occurs after irradiation, which is the most common complication and the major dose-limiting toxicity associated with radiotherapy. By limiting the radiation dose that can be applied and the size of the irradiated volume, RP hinders the tumor-controlling effects of radiotherapy [2, 3]. Furthermore, poor quality of life or life-threatening symptoms can be caused by RP in 15–40% of all patients who are irradiated for lung cancer [4]. Therefore, reliable predictors

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for RP occurrence is of great value to maximize the therapeutic effects and to minimize its adverse effects of RT. In addition to the previous reported patient- and treatment-related factors [5], including Karnofsky performance status (KPS), chronic lung disease [6], smoking status, chemotherapy [7, 8], dosimetric parameters and plasma values of TGF β [9, 10], some genetic variants were recently found to be associated with the occurrence and development of RP [11–16].

Homeodomain-interacting protein kinase 2 (*HIPK2*) is a member of serine/threonine kinase family. *HIPK2* plays important part in phosphorylation and interaction with a series of molecules involving development gene transcription and cellular responses to stress signals [17]. In addition, *HIPK2* regulates multiple transcription factors functioning in different processes including differentiation, apoptosis and proliferation [18]. Recently, the function of *HIPK2* in regulation of inflammation and fibrosis has drawn much attention. A study of idiopathic lung fibrosis (IPF) patients indicated that *HIPK2* gene defect was found in fibroblastic foci and such defect may result in phenotypic and biological behavioral change of fibroblasts and myofibroblasts [19]. The results provided evidences that dysfunction of *HIPK2* play significant role in disease progression and treatment resistance for IPF patients. However, up till now, the research on the function of *HIPK2* in RP risk and pathogenesis is lacking. *HIPK2* rs2030712 has been investigated as a potential risk factor of chronic kidney fibrotic disease occurrence and progression. Despite the fact that the study presented negative result [20], considering race disparities and different disease pathogenesis of RP, we selected rs2030712 as single nucleotide polymorphism (SNP) candidate for this study. In order to identify clinical valuable SNPs on RP occurrence and severity, in this study we explored the association between *HIPK2* SNP rs2030712 with RP risk in our cohort.

Methods

Patient population

Our prospective study was registered in ClinicalTrials.gov database (NCT02490319). In brief, 190 lung cancer patients were initially enrolled. All patients were treated with radiation therapy at Tongji Hospital, Huazhong University of Science and Technology (Wuhan, Hubei Province, China) between 2009 and 2015. We included the patients with a radiation dose at least 45 Gy, age > 18 years old, KPS > 60 and a life expectancy of at least 6 months. Patients with previous thoracic irradiation or severe cardiopulmonary diseases were excluded from our study. Of the 199 patients, 169 patients (114 with non-small cell lung cancer and 55 with small-cell lung cancer) were eventually included for the final genotyping analysis. Samples from 169

patients were genotyped by Sanger Sequencing for the SNP candidate. This study was approved by the Review Board of Tongji Hospital. Written informed consents were obtained from all patients for the use of their clinical information and for obtaining their blood and DNA.

Treatment and follow-up

All patients received radiotherapy with 6-MV X-rays from a linear accelerator (Elekta Synergy, Elekta, Sweden). The median total radiation dose was 56 Gy (range from 45 to 66 Gy), with 1.5 to 2 Gy administered per radiation treatment. IMRT (intensity-modulated radiation therapy) was administered to 46.7% of patients ($n = 79$). Computed tomography simulation (CT/e, GE, Fairfield, Connecticut, USA) was performed before the RT treatment was planned. The target volumes and critical normal organs were delineated by the three-dimensional planning system (Pinnacle Version 9.2). The baseline clinical characteristics and treatment details of the patients are shown in Table 1.

All patients enrolled in this study were examined during and one month after radiotherapy. Then, the patients were followed every three months for the first year and every six months thereafter. At each follow-up visits, all patients were asked to undergo a chest X-ray or CT and clinical information, including symptoms, was collected. RP was graded by two radiation oncologists (associate chief physician level required, with minimum 5 years of clinical experiences) according to the Common Terminology Criteria for Adverse Events 4.0 as follows: Grade 0, no change; Grade 1, asymptomatic and diagnosed by radiographic findings only; Grade 2, symptomatic, not interfering with daily activities; Grade 3, symptomatic, interfering with daily activities or oxygen required; Grade 4, assisted ventilation required; Grade 5, fatal.

Genotyping methods

Genomic DNA was extracted with a PureLink Genomic DNA Mini Kit (Invitrogen, K1820–01) from peripheral blood. *HIPK2*: rs2030712 was selected as single SNP candidate in this study, and was genotyped by Sanger Sequencing method for samples from 169 patients included. The primer pairs for rs2030712 were F: 5'-TGGAGATTTACAACACTCTAGGG-3'; R: 5'-ACA-GAACTCACGTGTGCTTT-3'. The 262 bp PCR products were then subjected to DNA sequencing to detect mutations.

Statistical analysis

The end point for this study was the development of RP \geq grade 2. The time to the end point was calculated from the start of radiotherapy. Patients who did not experience RP \geq grade 2 within 12 months of RT were

Table 1 Detailed clinical characteristics of the patients enrolled in this study ($N = 169$)

Characteristic	No. of Patients	%
Sex		
Male	125	74.0
Female	44	26.0
Age, years		
Median	58	
Range	28–78	
Histology		
SCLC	55	32.5
NSCLC	114	67.5
Stage		
I–II	24	10.2
III–IV	145	85.8
KPS		
80–100	123	72.6
< 80	46	27.4
Smoking		
Smoker	106	62.0
Non-smoker	63	38.0
Chemotherapy		
Yes	160	94.7
No	9	5.3
CRT		
Yes	44	26.0
No	125	74.0
Surgery		
Yes	86	50.9
No	83	49.1
IMRT		
Yes	79	46.7
No	90	53.3
Radiation dose (cGy)		
Median	5600	
Range	4500–6600	
MLD (cGy)		
Median	1368	
Range	178–2017	
V_{20}		
Median	24.82	
Range	0–42.00	
COPD		
Yes	19	11.2
No	150	88.8

Abbreviations: KPS Kamofsky performance status; CRT concurrent chemoradiation; IMRT intensity-modulated radiation therapy; MLD mean lung dose; V_{20} volume of normal lung receiving 20 Gy or more radiation; COPD chronic obstructive pulmonary disease

censored. SPSS 21.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for the statistically analysis. Patients were divided into groups according to their genotypes, and Cox proportional hazard analysis was applied to estimate the hazard ratio (HR) and 95% confidence intervals (CIs) of all factors possibly related to the risk of RP. Moreover, multivariable Cox regression analysis was used for the adjustment of covariates. The influences of the genotypes on RP risk were assessed by Kaplan-Meier analysis and compared with log-rank tests.

Results

Patient characteristics and radiation pneumonitis

One hundred sixty-nine patients were included in this study with 125 males and 44 females. Their characteristics are listed in Table 1. The median age of the population was 58 years (range from 28 to 78 years); 114 patients had NSCLC, and 55 had SCLC. In the study cohort, 85.5% of patients had stage III–IV disease, 50.9% underwent surgery before RT, almost all patients (94.7%) received induction chemotherapy followed by radiotherapy and 26.0% had concurrent chemoradiation. The median radiation dose was 56 Gy (range from 45 to 66 Gy), the median mean lung dosage (MLD) was 13.68 Gy (range from 1.78 to 20.17 Gy), and the median V_{20} was 24% (range from 0 to 42.00%).

Within 12 months of radiotherapy, 99 patients (58.6%) suffered RP \geq grade 2. The associations between patient-, tumor- and therapy-related characteristics and RP \geq grade 2 are listed in Table 2. The univariable and multivariable analysis by Cox regression model revealed that MLD and V_{20} was significantly related to RP \geq grade 2. Patients with elder age, MLD \geq 15Gy, $V_{20} \geq$ 24% had higher risk of RP \geq grade 2 compared with those counterparts (HR = 1.888, 95% CI: 1.186–3.004, $P = 0.007$; HR = 2.126, 95% CI: 1.338–3.378, $P = 0.001$, respectively) (Table 2), which were consistent with the results of other publications.

HIPK2 SNPs and RP

HIPK2: rs2030712 was found to be significantly associated with the occurrence of RP \geq grade 2 (Table 3). Figure 1 is a plot of the RP-free survival percentage for RP \geq grade 2 for each genotype of **HIPK2:** rs2030712 determined by the Kaplan-Meier method. Patients with the CC genotype of **HIPK2:** rs2030712 had significantly higher risks of RP \geq grade 2 than patients with CT genotype ($P < 0.0001$). Furthermore, multiple Cox proportional hazard analyses with adjustments for all of the characteristics listed in Table 1 revealed that the CC genotype of **HIPK2:** rs2030712 were strongly related to a increased occurrence of RP \geq grade 2 (HR = 2.146, 95% CI: 1.215–3.791, $P = 0.009$) (Table 3).

Table 2 Association between patient-, tumor-, and therapy-related characteristics and Grade ≥ 2 radiation pneumonitis ($N = 169$)

Parameter	Univariable Analysis			Multivariable Analysis		
	HR	95% CI	P	HR	95% CI	P
Sex						
Female	1			1		
Male	1.216	0.773–1.915	0.398	1.379	0.758–2.511	0.292
Age, years						
< 58	1			1		
≥ 58	1.413	0.951–2.098	0.087	1.541	0.997–2.383	0.052
Histology						
SCLC	1			1		
NSCLC	1.195	0.791–1.804	0.398	1.251	0.727–2.153	0.418
Stage						
I-II	1			1		
III-IV	1.100	0.601–2.013	0.758	1.132	0.593–2.163	0.707
KPS						
80–100	1			1		
< 80	1.341	0.877–2.052	0.176	1.566	0.993–2.470	0.054
Smoking						
Smoker	1			1		
Nonsmoker	0.926	0.619–1.386	0.708	0.964	0.337–2.192	0.435
Surgery						
Yes	1			1		
No	1.014	0.684–1.504	0.945	0.690	0.390–1.223	0.204
Chemotherapy						
Yes	1	1		1		
No	0.500	0.203–1.233	0.132	0.473	0.189–1.187	0.111
CRT						
Yes	1			1		
No	0.843	0.529–1.344	0.472	0.956	0.575–1.588	0.861
IMRT						
Yes	1			1		
No	1.077	0.726–1.598	0.712	1.098	0.710–1.699	0.675
Radiation dose, cGy						
< 5600	1			1		
≥ 5600	1.083	0.729–1.610	0.692	1.139	0.633–2.535	0.737
MLD, cGy						
< 1500	1			1		
≥ 1500	1.510	1.093–2.235	0.045	1.888	1.186–3.004	0.007
V20						
< 24%	1			1		
$\geq 24\%$	1.730	1.138–2.631	0.010	2.126	1.338–3.378	0.001
COPD						
Yes	1			1		
No	0.639	0.246–1.661	0.358	0.780	0.339–1.998	0.472

Note: Multivariable analyses were adjusted for all of the factors in this table, statistically significant p values for multivariable analysis were shown in boldface.
^aEither MLD or V20 was used in the multivariable analyses, but not both

Table 3 Association between genotypes and Grade ≥ 2 RP

Polymorphism and Genotype	No. of event	No. of total	Univariable analysis			Multivariable analysis		
			HR	95% CL	P	HR	95% CL	P
<i>HIPK2</i> : rs2030712								
CT	14	35	1			1		
CC	85	134	2.009	1.140–3.539	0.016	2.146	1.215–3.791	0.009

NOTE: Multiple analyses in this table were adjusted for all the factors listed in Table 1

Abbreviations: HR hazard ratio; CI confidence interval

Pc: P-value corrected by Benjamini and Hochberg False Discovery Rate correction

HIPK2: rs2030712 and Dosimetric factors

Patients were divided to four groups based on the dosimetric factors- V_{20} or MLD and *HIPK2*: rs2030712 genotypes in order to evaluate the impact of the *HIPK2*: rs2030712 genotypes on RP in different dosimetric groups. Patients with CC genotype of *HIPK2*: rs2030712 and MLD ≥ 15 Gy or $V_{20} \geq 24\%$ had the highest risk of RP grade ≥ 2 compared with other groups ($P < 0.0001$ and $P < 0.0001$, respectively, Fig. 2a, b). Interestingly, for the patients with *HIPK2*: rs2030712 CC genotype and MLD < 15 Gy or $V_{20} < 24\%$, they had even higher incidence of RP \geq grade 2 with the patients who received MLD more than 15Gy or V_{20} more than 24%, suggesting the dominant and independent role of *HIPK2*: rs2030712 genotypes in RP.

Discussion

In this study, *HIPK2*: rs2030712 were found for the first time to be significantly associated with the occurrence of RP \geq grade 2. Patients with the CC genotype of *HIPK2*: rs2030712 had a significantly increased risk of RP after radiotherapy for lung cancer. We also discovered that

the association between *HIPK2*: rs2030712 and RP grade ≥ 2 was independent of MLD and V_{20} .

The occurrences of RP \geq grade 2 were 58.6%, which were similar to those reported previously. Due to the prospective nature of our study, the incidence rate of RP was relatively higher than in some retrospective studies. We also confirmed that age, MLD and V_{20} was closely related to the risk of RP. In our cohort, patients with MLD ≥ 15 Gy and $V_{20} \geq 24\%$ had a greater risk of developing RP grade ≥ 2 , which verified the associations between the radiation dosimetric-related factors and the occurrence of RP.

As is well known that pro-inflammatory and fibrogenic cytokines induced by irradiation are involved in the pathogenesis of RP [21]. Our previous studies have already demonstrated that SNPs of several genes involving inflammation regulation are associated with RP risk [11–14]. However, the exact role that *HIPK2* playing in tissue inflammation and fibrosis is largely unknown. Recent advances in kidney fibrotic disease indicated that the protein expression of *HIPK2* was significantly elevated in human HIV- associated nephropathy patients [22]. In renal tubular epithelial cell model, study demonstrated that *HIPK2* not only up-regulated expression of several pro-fibrotic cytokines, such as smooth muscle actin, fibronectin, collagen I, but also activated several pro-fibrotic and pro-inflammatory signal pathways including TGF- β (transforming growth factor β)–Smad3, Wnt-Notch and NF- κ B pathways [23]. On the other hand, the role of *HIPK2* in pulmonary fibrotic disease, especially in RP is much less clear. Results from study on idiopathic pulmonary fibrosis (IPF) patients demonstrated that *HIPK2* expression in IPF-derived fibroblasts is significantly lower compared with normal counterparts [19]. In addition, allelic deletion was detected specifically in IPF fibroblast, which may be caused by chronic inflammation. This phenomenon was shown to be similar with precancerous lesion, which defective *HIPK2* was accumulated during clonal expansion of IPF fibroblast under inflammatory stimulus. Therefore, *HIPK2* may represent a novel therapeutic target in pulmonary fibrotic diseases.

Furthermore, in this study we demonstrated for the first time the prevalence and clinical value of *HIPK2*:

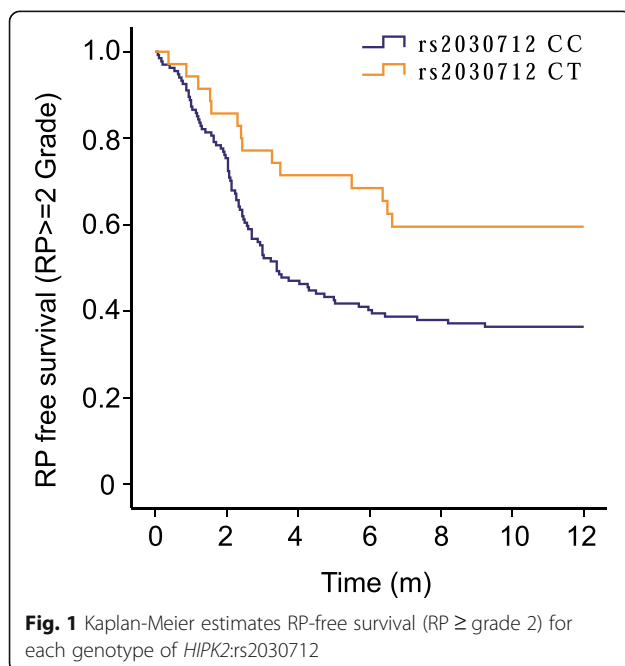


Fig. 1 Kaplan-Meier estimates RP-free survival (RP \geq grade 2) for each genotype of *HIPK2*:rs2030712

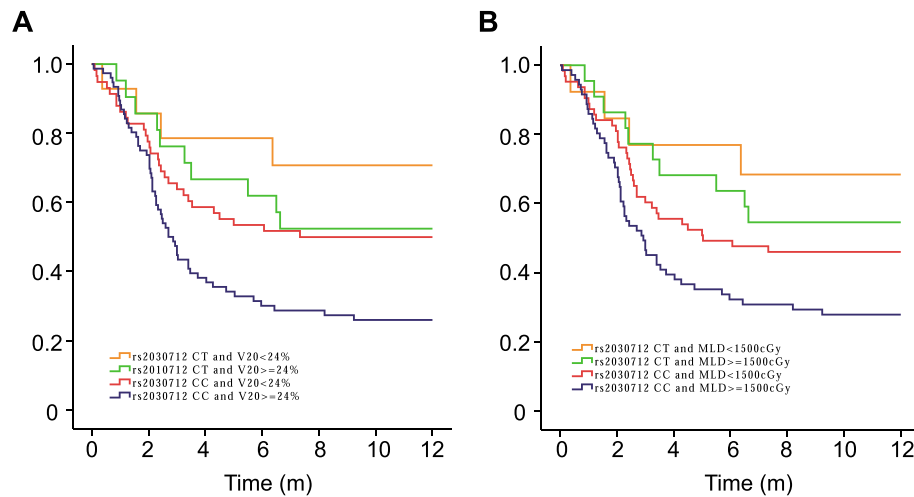


Fig. 2 Kaplan-Meier estimates effect of genotype in *HIPK2*:rs2030712 and dosimetric parameters on RP-free survival (RP ≥ grade 3) (a) *HIPK2*:rs2030712 and MLD; (b) *HIPK2*:rs2030712 and V_{20}

rs2030712 on RP in independent Chinese Han cohort, and may thus be one of the important predictors of severe RP before radiotherapy in addition to the radiation dosimetric factors. Those patients with RP susceptibility genotypes will greatly benefit from early prediction and prevention of RP by genotyping before the initiation of RT. And this study will help us to choose the patients without RP susceptibility genotypes and elevate their radiation dose appropriately for a better control of tumor. Especially for the patients with favorable genotypes, elevated MLD and V_{20} will not increase their incidence of severe RP, which could assist the oncologist to adjust the radiation dose personally. Moreover, our findings suggest the possible role of *HIPK2* in the pathogenesis of RP, which will aid in the discovery of target to treat RP in future research.

On the other hand, interstitial lung disease (ILD) is one of the risk factors that have been demonstrated to be related with increased RP incidence [24]. Unfortunately, in this study we didn't include the status of ILD as clinical parameter for cohort analysis, which had potential influence in our conclusion. Therefore, our results still require further validation in expanded cohorts with related ILD status information from different races, since the substantial ethnic variation exist in SNP frequencies. Moreover, *HIPK2*: rs2030712 warrant further investigation to identify the causative SNPs and their molecular mechanisms. Furthermore, we need to explore the potential role of *HIPK2* pathway in the pathogenesis of RP, which would provide novel insight into the treatment of RP.

Conclusions

In summary, it is the first study to confirm the associations between RP risk and *HIPK2*: rs2030712, and thus

indicated that in addition to the radiation dosimetric factors, *HIPK2* SNP can be used as useful predictive biomarker of RP risk before RT. Thus, patients will greatly benefit from early prediction and prevention of RP by genotyping before the initiation of RT. And this study will benefit lung cancer patients receiving radiotherapy since appropriately tailored radiation dose might result in better control of their diseases and lower occurrence and severity of RP.

Abbreviations

IPF: Idiopathic pulmonary fibrosis; KPS: Karnofsky performance status; MLD: Mean lung dosage; NSCLC: Non small cell lung cancer; RP: Radiation pneumonitis; RT: Radiotherapy; SCLC: Small cell lung cancer; SNP: Single nucleotide polymorphism

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Not applicable.

Authors' contributions

TY designed and conducted the major analytical work of the study; YL wrote the draft of the manuscript; QW, YMX and LB contributed in the data collection and statistical analysis. YXL supervised the whole study conduction; All authors have read and approved the final manuscript.

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Availability of data and materials

The detailed genetic data from our cohort analyzed during the current study are not publicly available due to the private gene information protection policy of our center. But they are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was approved by the Review Board of Tongji Hospital. Written informed consents were obtained from all patients for the use of their clinical information and for obtaining their blood and DNA.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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