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Research article

Investigation of *RBM10* mutation and its associations with clinical and molecular characteristics in *EGFR*-mutant and *EGFR*-wildtype lung adenocarcinoma

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ABSTRACT

Background: RBM10 is commonly mutated in lung adenocarcinoma (LUAD). However, its role in the pathogenesis of LUAD remains undefined. *EGFR*-mutant LUAD represents a distinct subset of non-small cell lung cancer (NSCLC). The function of *RBM10* in tumor pathogenesis is supposed to differ between *EGFR*-mutant and *EGFR*-wt LUAD. This study aimed to interrogate the prevalence of *RBM10* mutation in a large cohort of Chinese patients with LUAD and investigate the association of *RBM10* mutation with clinical and molecular characteristics of *EGFR*-mutant and *EGFR*-wt LUAD.

Methods: Tumor sequencing data from 2848 Chinese patients with LUAD were retrospectively reviewed and analyzed. The prevalence of *RBM10* was also compared with other three cohorts: OrigMed (n = 1222), MSKCC (n = 1267), and TCGA (n = 566). The associations of *RBM10* mutation with clinical and molecular characteristics were assessed. An external cohort of 182 patients with LUAD who received PD-1 inhibitor were used to investigate the association of *RBM10* mutation with clinical outcomes upon immunotherapy.

Results: Our cohort showed a higher prevalence of *RBM10* in *EGFR*-mutant LUAD than in *EGFR*-wt LUAD (14.8 % vs. 6.5 %, $p < 0.001$). The enrichment of *RBM10* mutations in *EGFR*-mutant LUAD was also seen in another Chinese cohort (OrigMed: 14.9 % vs. 7.8 %, $p < 0.001$), but not in the two western cohorts (MSKCC: 7.4 % vs. 9.5 %, $p = 0.272$; TCGA: 8.1 % vs. 6.7 %, $p = 0.624$). *RBM10* mutations co-occurred more frequently with *EGFR* L858R mutations (23.7 %) than with other types of *EGFR* mutations (19 del: 7.7 %; other: 7.1 % in others, $p < 0.001$). In *EGFR*-mutant LUAD, *RBM10* mutations were more commonly found in stage I (18.2 %) and II (21.8 %) vs. stage III (9.4 %) and IV (11.3 %) tumors ($p < 0.001$). The proportion of PD-L1 positive expression in *EGFR*-mutant LUAD with concomitant *RBM10* mutation was not different from that those without *RBM10* mutations (41.8 % vs. 47.9 %, $p = 0.566$). In contrast, *RBM10* mutation occurred more frequently in *EGFR*-wt LUAD at stage II-IV (stage II: 12.0 %, stage III: 8.7 %, stage IV: 6.6 %) than at stage I (2.8 %). *EGFR*-wt LUAD with concomitant *RBM10* mutations had higher proportions of

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PD-L1 expression positivity (78.9 % vs. 61.9 %, p = 0.014) and higher tumor mutational load (8.97 vs. 2.99 muts/Mb, p < 0.001) than those without. Patients with *EGFR*-wt LUAD who also harbored *RBM10* loss of function (LOF) mutations had a longer median PFS upon immunotherapy than those with *RBM10* non-LOF mutations (7.15 m vs. 2.60 m, HR = 4.83 [1.30–17.94], p = 0.010).

Conclusion: We comprehensively investigated *RBM10* mutations in a Chinese cohort with LUAD. Compared to western cohorts, a significant enrichment of RBM10 mutations in EGFR-mutant LUAD compared to EGFR-wildtype LUAD in the Chinese population. *RBM10* mutation shows different associations with clinical and molecular characteristics between *EGFR*-mutant and *EGFR*-wt LUAD, suggesting a divergent mechanism between these two subsets via which *RBM10* deficiency contribute to tumor pathogenesis. The findings contribute to our understanding of the molecular landscape of LUAD and highlight the importance of considering population-specific factors in cancer genomics research.

1. Introduction

RBM10 encode a nuclear RNA-binding protein (RBP). It regulates the alternative splicing of primary transcripts and is also involved in other molecular and biological processes, such as post-transcriptional regulation, p53 stabilization, cell cycle arrest, and anti-viral reactions [1]. *RBM10* is commonly mutated in lung adenocarcinoma (LUAD) with the prevalence ranging from 7 % to 22 % [2–5] reported in different studies. However, its function in LUAD remains undefined. Some studies have revealed that overexpression of *RBM10* reduces cell proliferation and promotes apoptosis [6,7], while deficiency in *RBM10* contributes to LUAD pathogenesis [8], implying its role as a tumor suppressor. Conversely, results from other studies suggest *RBM10* may function as an oncogene in lung adenocarcinoma [8]. A recent study reported that *RBM10* deficiency decreased *EGFR* inhibitor efficacy in *EGFR*-mutant tumors by diminishing *EGFR* inhibitor-mediated apoptosis. The authors also showed that *RBM10* deficiency was a biomarker of poor response to *EGFR* inhibitor treatment in patients with LUAD [9]. On the other hand, *RBM10* deficiency has also been associated with increased anti-tumor immunity in LUAD [10], suggesting its potential predictive value for immunotherapy.

EGFR-sensitizing mutations have been identified in 30–35 % of lung small cell lung cancer (NSCLC) in Asian populations and in 10–15 % of Caucasian patients with NSCLC [11]. *EGFR*-mutant LUAD represents a subset of NSCLC with distinctive molecular and clinical characteristics. Conceivably, the function of *RBM10* in tumor pathogenesis may largely differ between *EGFR*-mutant and *EGFR*-wt LUAD. However, relevant data is scarce. In the present study, we sought to interrogate the prevalence of *RBM10* mutation in a large cohort of Chinese patients with LUAD and investigate the association of *RBM10* mutation with molecular and clinical characteristics of *EGFR*-mutant and *EGFR*-wt LAUD.

2. Materials and methods

2.1. Patients' information

A total of 2848 patients with LUAD, who underwent tumor sequencing from January 2020 to April 2023 were retrospectively included in the study. The inclusion criteria included: 1) Patients were sequenced in Burning Rock Biotech, a Clinical Laboratory Improvement Amendments (CLIA)/College of American Pathologists (CAP)-certified laboratory; 2) Sequencing was performed using a 520 gene-panel; 3) Sequencing was performed with tumor tissue or formalin fixed paraffin-embedded (FFPE) samples collected at baseline before treatment was administrated; 4) Pathologically confirmed lung adenocarcinoma. DNA sequencing data, PD-L1 expression results, and patients' clinical and demographic characteristics were retrospectively reviewed and analyzed. DNA sequencing data of OrigMed (n = 1222) [12], MSKCC (n = 1267) [13], and TCGA (n = 566) [14] cohorts of patients with LUAD were also downloaded from cBioPortal (https://www.cbioportal.org) and analyzed for comparison. A total 182 patients with LUAD from lung_msk_mind_2020 cohort [15] who received PD-1 inhibitor or PD-1 plus CTL4 inhibitors were included for survival analysis. Progressive-free survival (PFS) data was retrieved.

2.2. Next-generation sequencing

DNA was extracted and subjected to capture-based DNA sequencing using a panel including 520 cancer-related genes (Oncoscreen plus, Burning Rock Biotech, Guangzhou, China). Sequencing data was analyzed using established variant calling pipelines optimized for identifying somatic variants as described previously [16]. Variants with a frequency >0.1 % in the database of ExAC, 1000 Genomes, dbSNP, or ESP6500SI–V2 were excluded. The remaining variants were annotated with ANNOVAR (2016-02-01 release) [17] and SnpEff v.3.6 [18]. Stuctural variation was analyzed using an in-house script markSV. The copy number variation (CNV) was estimated with an in-house algorithm based on the sequencing depth as described previously [19]. Tumor mutational burden (TMB) was calculated for a given sample as the ratio between the number of detected somatic mutations with the total size (1.003 Mb) of the coding region of the panel. The mutation count included non-synonymous single nucleotide variants (SNVs) and small insertion-deletion variants (Indels) detected within the coding region and ±2bp upstream or downstream region and does not include hot mutation events, CNVs, SVs, and germline SNPs.

2.3. PD-L1 expression assessment

PD-L1 expression was assessed by immunohistochemistry 22C3 pharmDx assay (Agilent Technologies) and measured using TPS, which is defined as the percentage PD-L1 stained viable tumor cells at any intensity. TPS>1 % was considered as PD-L1 positivity.

2.4. Statistical analysis

Statistical analyses were performed using R version 4.2.3 software. Differences in the groups were calculated and presented using Fisher's exact test, paired two-tailed Student's t-test, or analysis of variance as appropriate. Kaplan-Meier analysis was used to estimate survival, and a log-rank test was used to determine the differences in the multiple survival metrics between groups. p-values <0.05 were considered statistically significant.

3. Results

3.1. Enrichment of RBM10 mutations in EGFR-mutant LUAD in the Chinese population

Of the 2848 patients with LUAD from the Burning Rock (BR) database, 312 (11.0 %) harbored *RBM10* mutations. The prevalence was 14.8 % in the *EGFR*-mutant group and only 6.5 % in the *EGFR*-wt group ($p < 0.001$, Fig. 1A). In another Chinese cohort with LUAD (OrigMed), the prevalence was also significantly higher in the *EGFR*-mutant group than in the *EGFR*-wt group (14.9 % vs. 7.8 %, $p < 0.001$, Fig. 1B). Interestingly, the prevalence of *RBM10* mutations was comparable between *EGFR*-mutant and -wt LUAD in the two Western cohorts (MSKCC: 7.4 % vs. 9.5 %, $p = 0.272$, Fig. 1C; TCGA: 8.1 % vs. 6.7 %, $p = 0.624$, Fig. 1D).

As illustrated in Fig. S1A, no hot spot mutations were seen for *RBM10* mutations. Loss of function (LOF) mutations, including stop gained, splice site, and frameshift mutations, comprised the majority of the *RBM10* mutations, irrespective of racial difference; while the proportion LOF mutations was slightly higher in the two Chinese cohort than in the two Western cohort (Fig. S1B). In the two Chinese cohorts, *RBM10* mutations in the *EGFR*-mutant LUAD showed a significantly higher proportion of LOF type than in the *EGFR*-wt group (BR: 92.0 % vs. 70.9 %, $p < 0.001$, Fig. 1E; OrigMed: 88.6 % vs. 72.5 %, $p = 0.023$, Fig. 1F). Interestingly, such difference was

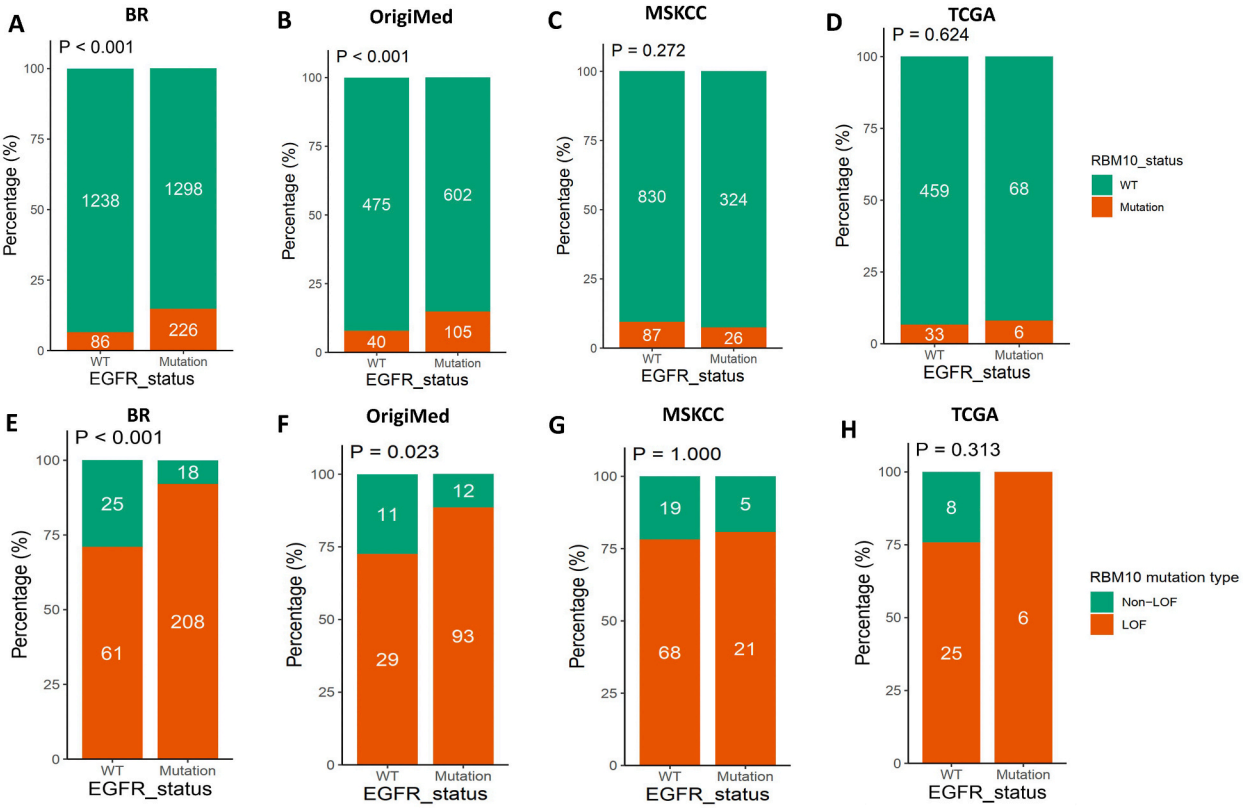

Fig. 1. Comparsion of *RBM10* mutations between *EGFR*-mutant and wildtype NSCLC from different databases. A (Burning Rock (BR)) and B (OrigiMed) : In the two Chinese cohorts , RBM10 mutations were significantly higher in the EGFR mutant group than EGFR-WT group ($p < 0.001$); C (MSKCC) and D (TCGA) : In the two West cohorts , the prevalence of RBM10 mutations was comparable between EGFR-mutant and -wt LUAD. (E–H) Proportion of *RBM10* loss of function (LOF) mutations. E:Burning Rock (BR) cohorts,F: OrigiMed,G:MSKCC,H:TCGA.

not observed in the two Western LUAD cohorts (Fig. 1G&H).

3.2. *RBM10* mutation and association with clinical and molecular characteristics in EGFR-mutant LUAD

Next, we interrogated the *RBM10* mutations that co-occurred with different types of *EGFR* mutations. *EGFR* L858R, 19 exon deletion (19 del), and T790 M were identified in 45 %, 40 %, and 2 % of BR LUAD cohort and 21 % of patients harbored other *EGFR* mutations (Fig. 2A). We observed a significantly higher frequency of *RBM10* mutations co-occurring with *EGFR* L858R mutations (23.7 %) than with other types of *EGFR* mutations (7.7 % in 19 del, 7.1 % in others, $p < 0.001$) (Fig. 2B). Nearly a quarter of patients (16.2 %) with L858R and 19 del carry *RBM10* mutations. Moreover, 93.3 % of in the *RBM10* mutations co-occurring with L858R were LOF, higher that the LOF proportion in those co-occurring with *EGFR* 19 del (87.2 %) and other *EGFR* mutations (93.8 %) ($p = 0.353$) (Fig. 2C).

In *EGFR*-mutant LUAD, we observed higher prevalence of *RBM10* mutations in stage I (18.2 %) and II (21.8 %) vs. stage III (9.4 %) and IV (11.3 %) tumors ($p < 0.001$, Fig. 3A). The prevalence was not significantly different between female and male (14.9 % vs. 13.9 %, $p = 0.638$, Fig. 3B). *RBM10* mutation was also associated with an older age of onset in *EGFR*-mutant LUAD ($p < 0.001$, Fig. 3C).

The molecular features, EGFR-mutant LUAD with RBM10 mutations exhibit a slightly lower proportion of PD-L1 expression (41.8 %) compared to those without RBM10 mutations (47.9 %) ($p = 0.566$, Fig. 3D). Tumors with *RBM10* LOF mutations had a slightly lower proportion of PD-L1 positivity (40.5 %) than *RBM10*-wt (47.9 %) and *RBM10* non-LOF mutant tumors (57.1 %) ($p = 0.391$, Fig. 3E). We also compared the TMB among groups with different *RBM10* mutations status. *EGFR*-mutant LUAD with *RBM10* mutations had higher TMB than those without *RBM10* mutations (2.99 vs. 1.99 muts/Mb, $p < 0.001$, Fig. 3F). At the same time, regardless of whether RBM10 is LOF variant or non-LOF variant, their TMB had higher than that of RBM10 wild-type EGFR mutant LUAD (Fig. 3G).

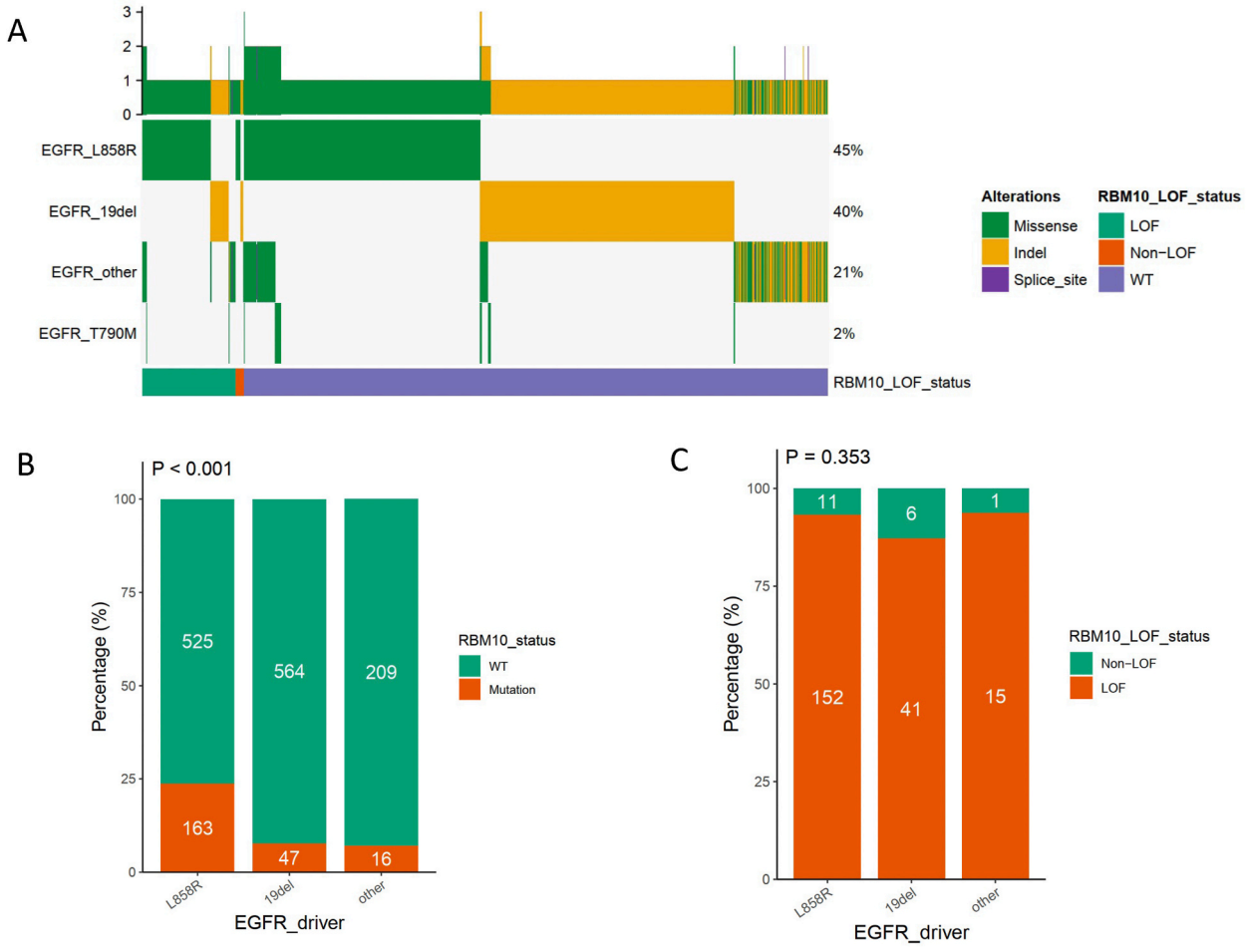

Fig. 2. *RBM10* mutations in *EGFR*-mutant NSCLC. (A) Oncoprint showing the status of RBM10 mutations in *EGFR*-mutant NSCLC. (B) Rate of *RBM10* mutations among NSCLC with different *EGFR* mutations. (C) Rate of LOF *RBM10* mutations among NSCLC with different *EGFR* mutations.

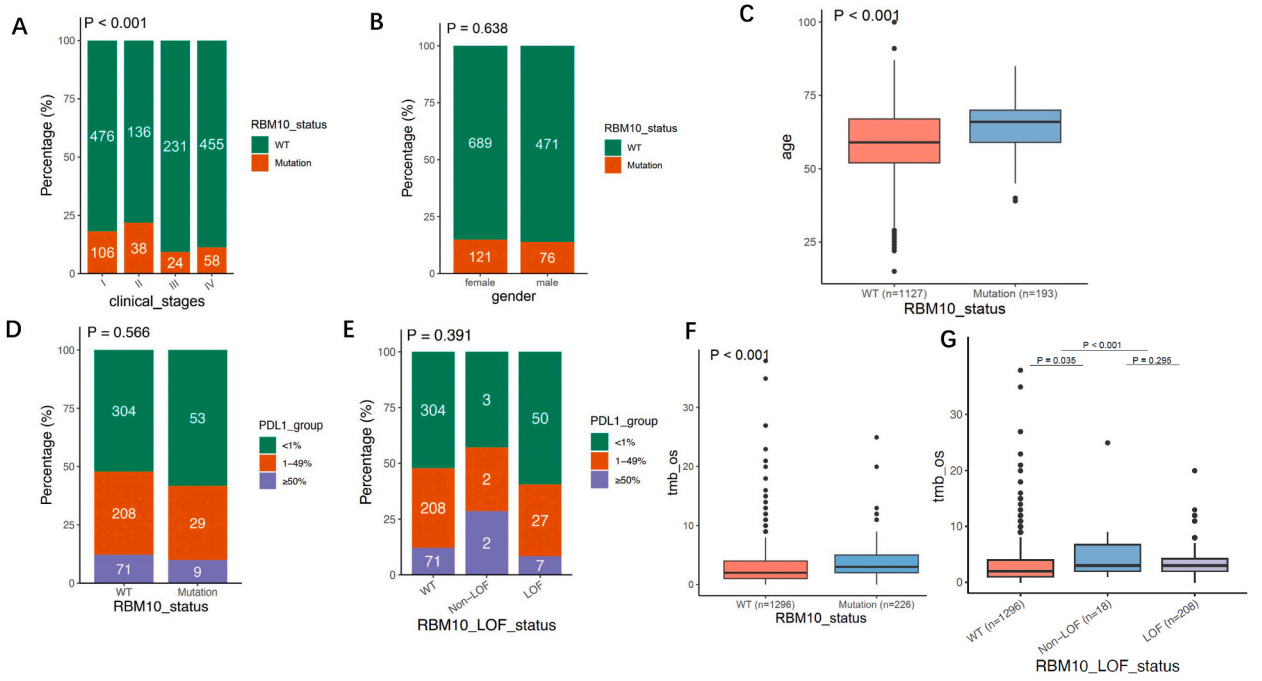

Fig. 3. Associations of *RBM10* mutations with clinical and molecular characteristics in *EGFR*-mutant NSCLC of BR cohort. (A) Differences in RBM10 mutations by clinical stage. (B) Differences in RBM10 mutations by Sex. (C) Differences in RBM10 mutations by Age. (D) Differences in RBM10 mutations by PD-L1 expression. (E) Differences in RBM10 LOF stauts by PD-L1 expression. (F) Differences in RBM10 mutations by TMB. (G) Differences in RBM10 LOF stauts by TMB.

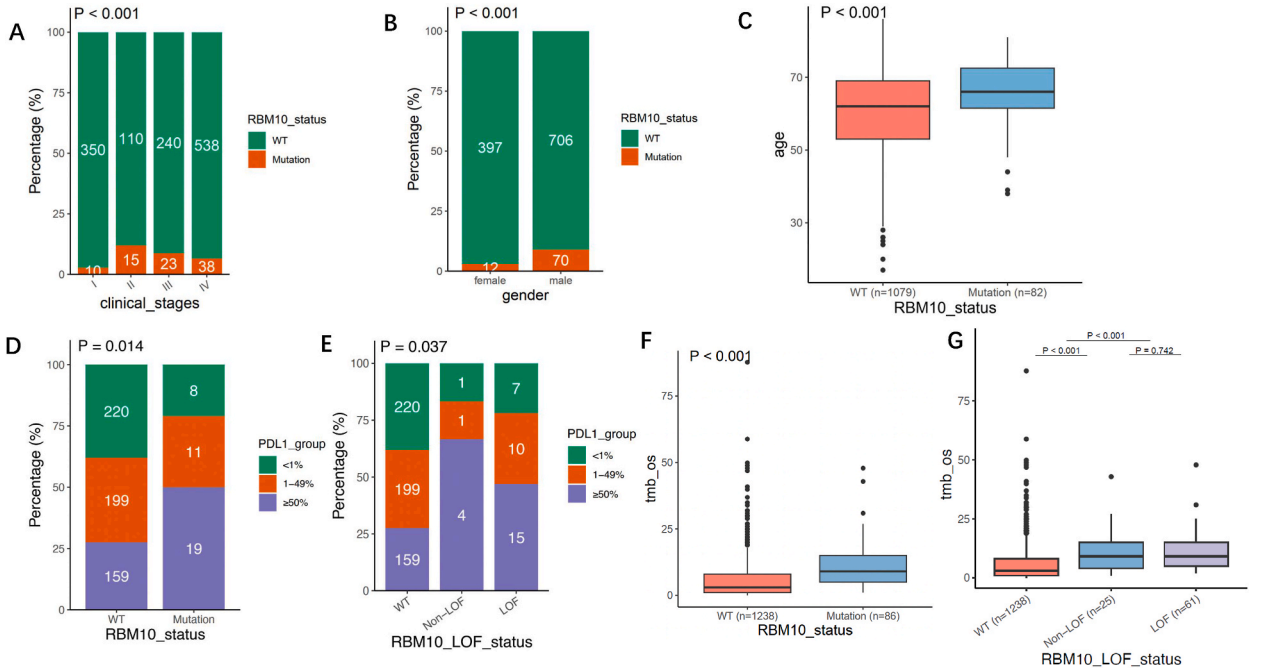

Fig. 4. Associations of RBM10 mutations with clinical and molecular characteristics in *EGFR*-wt NSCLC of BR cohort. (A) Differences in RBM10 mutations by clinical stage. (B) Differences in RBM10 mutations by Sex. (C) Differences in RBM10 mutations by Age. (D) Differences in RBM10 mutations by PD-L1 expression. (E) Differences in RBM10 LOF stauts by PD-L1 expression. (F) Differences in RBM10 mutations by TMB. (G) Differences in RBM10 LOF stauts by TMB.

3.3. The association of *RBM10* mutations with clinical and molecular characteristics in *EGFR*-wt LUAD

Next, we investigated the association of *RBM10* mutations with clinical and molecular characteristics in *EGFR*-wt LUAD. In contrast to *EGFR*-mutant LUAD, *EGFR*-wt LUAD revealed higher prevalence of *RBM10* mutations at stage II-IV (stage II: 12.0 %, stage III:8.7 %, stage IV:6.6 %) than at stage I (2.8 %) (Fig. 4A, $p < 0.001$). We also observed significant associations of *RBM10* mutations with male ($p < 0.001$, Fig. 4B) and an older onset age ($p < 0.001$, Fig. 4C). Interestingly, *RBM10* showed an opposite association with PD-L1 expression in *EGFR*-wt LUAD compared to *EGFR*-mutant LUAD. *EGFR*-wt LUAD that harbored concomitant *RBM10* mutations had higher proportions of PD-L1 expression positivity and PD-L1 higher expression (TPS≥50 %) than those without *RBM10* mutations (78.9 % vs. 61.9 %, 50.0 % vs. 27.5 %, $p = 0.014$) (Fig. 4D). The proportion of PD-L1 positivity was similar between *RBM10* LOF (78.1 %) and non-LOF (83.3 %) subsets, and both were higher than that in the *RBM*10-wt group ($p = 0.037$) (Fig. 4E). The *RBM10* LOF subset revealed a higher proportion of high PD-L1 expression (TPS≥50 %) (46.9 %) than the *RBM10*-wt group (27.5 %) ($p = 0.026$), while the difference was not significant compared with the *RBM10* non-LOF subset (46.9 vs. 66.7 %, $p = 0.660$). The TMB analysis showed a higher mutation load in the *RBM10*-mutant than *RBM10*-wt group (8.97 vs. 2.99 muts/Mb, $p < 0.001$, Fig. 4F). The TMB was comparable between *RBM10* LOF and *RBM10* non-LOF subsets (8.97 vs. 8.97, $p = 0.742$, Fig. 4G).

We also compared the TMB among groups with different *RBM10* mutations status. *EGFR*-mutant LUAD with *RBM10* mutations had higher TMB than those without *RBM10* mutations (2.99 vs. 1.99 muts/Mb, $p < 0.001$, Fig. 3F). At the same time, regardless of whether RBM10 is LOF variant or non-LOF variant, their TMB had higher than that of RBM10 wild-type EGFR mutant LUAD (Fig. 3G).

3.4. *RBM10* mutation status and survival in patients with *EGFR*-wt LUAD treated with PD1 inhibitors

Finally, we exploratorily investigated the association of *RBM10* mutation status with PFS in an external cohort of 178 EGFR-wt LUAD patients who received PD-1 inhibitor or PD-1 plus CTL4 inhibitors. Patients with *RBM10* mutations did not show significantly differential PFS compared with patients without *RBM10* mutation, regardless of mutation type (Fig. 5A, $p = 0.37$ for LOF, $p = 0.1$ for non-LOF). However, patients with *RBM10* LOF mutations had a longer median PFS than those with *RBM10* non-LOF mutations (7.15 m vs. 2.60 m, HR = 4.83 [1.30–17.94], $p = 0.010$, Fig. 5B).

4. Discussion

Our study, for the first time, revealed that *RBM10* mutations co-occurred preferably with *EGFR* mutations only in the Chinese population, not in the Western population. This ethnical difference may suggest divergent functions of *RBM10* mutations involved in the development of *EGFR*-mutant lung cancer in different populations. Moreover, the higher proportion of LOF mutation type in the *EGFR*-mutant LUAD than in the *EGFR*-wt LUAD further supports these *RBM10* mutations are not messenger events in Chinese patients with *EGFR*-mutant LUAD. In a recent study, loss of *RBM10* was found to be mutually exclusive with mutations in the tumor suppressor gene TP53, promote tumorigenesis, and enhances the efficacy of spliceosome inhibition in *EGFR*-driven lung cancer [20]. Another study showed that *RBM10* deficiency in *EGFR* mutant LUAD decreases the apoptotic response to *EGFR* inhibitor, resulting in tumor progression during *EGFR* TKI treatment and inferior clinical outcomes [9]. Interestingly, Zhang et al. reported that *RBM10* mutations mostly co-occurred with mutations in *EGFR* and *KRAS* in a Chinese and the TCGA LUAD cohorts, respectively, indicating the contribution of *RBM10* mutations to LUAD pathogenesis with distinct genetic backgrounds in different ethnical populations [21]. We

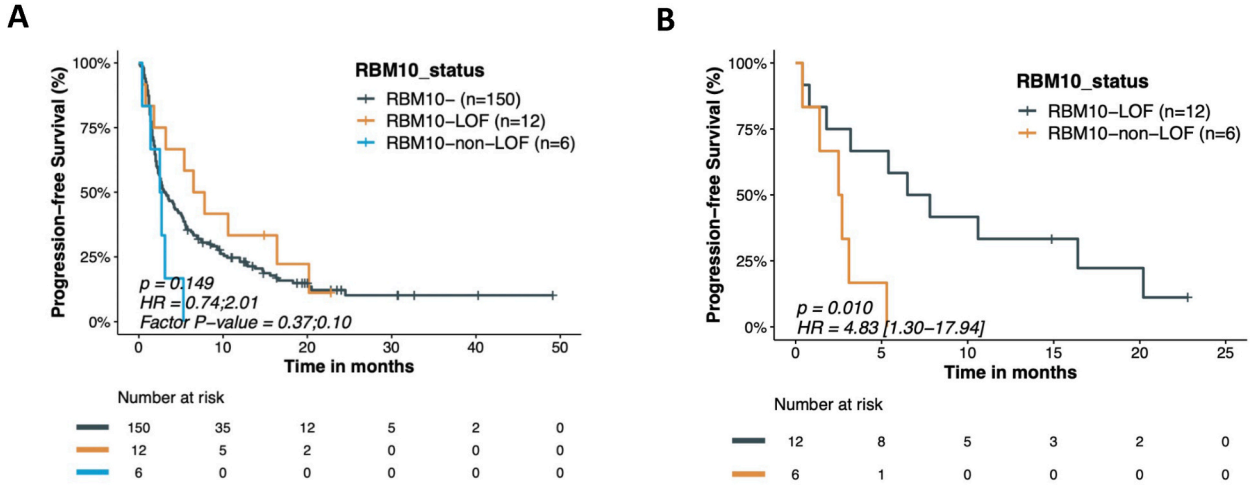

Fig. 5. Association of *RBM10* mutation status with PFS in patients with *EGFR*-wt LUAD who was treated with PD-1 inhibitor. (A)Comparison of PFS between patients with *RBM10* LOF or non-LOF mutation and those without *RBM10* mutations. (B)Comparison of PFS between patients with *RBM10* LOF vs. non-LOF mutations.

also observed that *RBM10* mutations preferably co-occurred with *EGFR* L858R as compared with 19del (23.7 vs. 7.7 %). This is consistent with a previous report in a Western population, where the frequency of *RBM10* truncating mutations was 15 % in the L858R subset vs. 3 % in the 19del subset [9]. This might explain the observation that patients with *EGFR* L858R generally have worse clinical outcomes than patients with *EGFR* 19 del [22], given that *RBM10* deficiency limits therapeutic response to *EGFR* inhibitors [9]. However, how or why *RBM10* mutations are enriched in *EGFR*-mutant LUAD of Chinese population and in the *EGFR* L858R mutant subtype remains unexplained and merits future investigation.

We also observed distinct associations of *RBM10* mutations with clinical/molecular characteristics in *EGFR*-wt vs. *EGFR*-mutant LUAD. *RBM10* mutation was more frequently detected in older patients irrespective of *EGFR* mutation status, while it was mutated more frequently in male patients than females only in *EGFR*-wt LUAD. Moreover, *RBM10* mutation was more enriched in earlier stage of *EGFR*-mutant LUAD but more frequently seen in later stage of *EGFR*-wt LUAD. Functional studies have showed that *RBM10* inhibits cell proliferation, metastasis and EMT progression in LUAD [23]. Our results suggest that *RBM10* loss of function may contribute to the progression of *EGFR*-wt LUAD by promoting EMT and metastasis. In *EGFR*-mutant LUAD, it may function via a different mechanism (etc. as a tumor suppressor akin to p53 as reported by Bao et al. [20]). Wu et al. have reported *RBM10* mutations in 30 % (9/30) of ground-glass nodules (GGNs) and GGNs with *RBM10* mutations tended to have a pathologically lepidic pattern [24]. Notably, 8/9 of these *RBM10*-mutant GGNs also harbored concomitant *EGFR* mutations, indicating *RBM10* may drive the distinct pathologic subtype of *EGFR*-mutant LUAD.

Our results also showed that *RBM10* mutation was associated with higher PD-L1 expression and higher tumor mutational load in *EGFR*-wt LUAD, regardless of *RBM10* mutation status. Unfortunately, we failed to observe significantly longer PFS in *RBM10* mutant patients with *EGFR*-wt LUAD than those without *RBM10* mutations upon treatment with PD-1 inhibitor in an external cohort (Fig. 5A). Interestingly, the *RBM10* LOF subgroup had significantly longer PFS than the non-LOF group (Fig. 5B), however no difference in PD-L1 expression or TMB was seen between the two groups in the BR cohort. Notably, the results should be interpreted with cautions since the sample the size of the external cohort is too small. Alternatively, it is possible that other immune-relevant factors, such as tumor infiltrating lymphocytes, might affect the efficacy of immunotherapy. Actually, Liu et al. have showed that LUADs with *RBM10* deficiency had higher infiltration levels for myeloid dendritic cells, macrophages, neutrophils and CD8+T cells, and increased immune activity [10]. Of note, the cohort in their study included both *EGFR*-mutant and *EGFR*-wt LUAD. Interestingly, in contrast to *EGFR*-wt LUAD, we found an association between *RBM10* mutation and lower PD-L1 expression in *EGFR*-mutant LUAD. The explanation for this observation is unknown, which however again suggest a different role of *RBM10* deficiency in the pathogenesis of *EGFR*-mutant LUAD compared to *EGFR*-wt tumors.

Conclusion: We comprehensively investigated *RBM10* mutations in a Chinese cohort with LUAD. Our results revealed a Chinese population-specific enrichment of *RBM10* mutations in *EGFR*-mutant LUAD. *RBM10* mutation shows different associations with clinical and molecular characteristics between *EGFR*-mutant and *EGFR*-wt LUAD, suggesting a divergent mechanism between these two subsets via which *RBM10* deficiency contribute to tumor pathogenesis.

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Ethical statement

This study was performed according to the Declaration of Helsinki in 1964 and its current amendments. Written informed consent was obtained from all patients before genetic analysis of biological samples. The study was approved by the Ethics Committee of Cancer Hospital & Shenzhen Hospital, Chinese Academy of Medical Sciences (YW2023-46-1).

Data availability statement

Raw sequencing data of the BR-cohort have been deposited in the OMIX, China National Center for Bioinformation (https://ngdc.cncb.ac.cn/omix: accession no. OMIX005280) and can be obtained by request to the corresponding author.

CRediT authorship contribution statement

Yingyue Cao: Writing – original draft, Supervision, Data curation, Conceptualization. **Dongmei Lan:** Writing – review & editing, Writing – original draft, Data curation. **Xianni Ke:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis. **Wenyu Zheng:** Writing – review & editing, Methodology, Formal analysis. **Jialong Zeng:** Writing – review & editing, Software, Formal analysis. **Niu Niu:** Visualization, Methodology. **Chunmei Fu:** Writing – review & editing, Software, Methodology, Investigation. **Wencui Deng:** Writing – review & editing, Visualization, Validation. **Shi Jin:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to

influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e32287.

References

[1] A. Inoue, RBM10: structure, functions, and associated diseases, Gene 783 (May 30 2021) 145463, https://doi.org/10.1016/j.gene.2021.145463.
[2] M. Imielinski, A.H. Berger, P.S. Hammerman, et al., Mapping the hallmarks of lung adenocarcinoma with massively parallel sequencing, Cell 150 (6) (Sep 14 2012) 1107–1120, https://doi.org/10.1016/j.cell.2012.08.029.
[3] N. Cancer Genome Atlas Research, Comprehensive molecular profiling of lung adenocarcinoma, Nature 511 (7511) (Jul 31 2014) 543–550, https://doi.org/10.1038/nature13385.
[4] C. Vinayanuwattikun, F. Le Calvez-Kelm, B. Abedi-Ardekani, et al., Elucidating genomic characteristics of lung cancer progression from in situ to invasive adenocarcinoma, Sci. Rep. 6 (Aug 22 2016) 31628, https://doi.org/10.1038/srep31628.
[5] L.L. Yin, X.M. Wen, M. Li, et al., A gene mutation in RNA-binding protein 10 is associated with lung adenocarcinoma progression and poor prognosis, Oncol. Lett. 16 (5) (Nov 2018) 6283–6292, https://doi.org/10.3892/ol.2018.9496.
[6] G. Guan, R. Li, W. Tang, et al., Expression of RNA-binding motif 10 is associated with advanced tumor stage and malignant behaviors of lung adenocarcinoma cancer cells, Tumour Biol 39 (3) (Mar 2017) 1010428317691740, https://doi.org/10.1177/1010428317691740.
[7] J.H. Jung, H. Lee, B. Cao, P. Liao, S.X. Zeng, H. Lu, RNA-binding motif protein 10 induces apoptosis and suppresses proliferation by activating p53, Oncogene 39 (5) (Jan 2020) 1031–1040, https://doi.org/10.1038/s41388-019-1034-9.
[8] J. Zhao, Y. Sun, Y. Huang, et al., Functional analysis reveals that RBM10 mutations contribute to lung adenocarcinoma pathogenesis by deregulating splicing, Sci. Rep. 7 (Jan 16 2017) 40488, https://doi.org/10.1038/srep40488.
[9] S. Nanjo, W. Wu, N. Karachaliou, et al., Deficiency of the splicing factor RBM10 limits *EGFR* inhibitor response in *EGFR*-mutant lung cancer, J. Clin. Invest. 132 (13) (Jul 1 2022), https://doi.org/10.1172/JCI145099.
[10] B. Liu, Y. Wang, H. Wang, et al., RBM10 deficiency is associated with increased immune activity in lung adenocarcinoma, Front. Oncol. 11 (2021) 677826, https://doi.org/10.3389/fonc.2021.677826.
[11] S.V. Sharma, D.W. Bell, J. Settleman, D.A. Haber, Epidermal growth factor receptor mutations in lung cancer, Nat. Rev. Cancer 7 (3) (Mar 2007) 169–181, https://doi.org/10.1038/nrc2088.
[12] L. Wu, H. Yao, H. Chen, et al., Landscape of somatic alterations in large-scale solid tumors from an Asian population, Nat. Commun. 13 (1) (Jul 23 2022) 4264, https://doi.org/10.1038/s41467-022-31780-9.
[13] A. Zehir, R. Benayed, R.H. Shah, et al., Mutational landscape of metastatic cancer revealed from prospective clinical sequencing of 10,000 patients, Nat. Med. 23 (6) (Jun 2017) 703–713, https://doi.org/10.1038/nm.4333.
[14] K.A. Hoadley, C. Yau, T. Hinoue, et al., Cell-of-Origin patterns dominate the molecular classification of 10,000 tumors from 33 types of cancer, Cell 173 (2) (Apr 5 2018) 291–304 e6, https://doi.org/10.1016/j.cell.2018.03.022.
[15] R.S. Vanguri, J. Luo, A.T. Aukerman, et al., Multimodal integration of radiology, pathology and genomics for prediction of response to PD-(L)1 blockade in patients with non-small cell lung cancer, Nat. Can. (Ott.) 3 (10) (Oct 2022) 1151–1164, https://doi.org/10.1038/s43018-022-00416-8.
[16] M. Wang, X. Chen, Y. Dai, et al., Concordance study of a 520-gene next-generation sequencing-based genomic profiling assay of tissue and plasma samples, Mol. Diagn. Ther. 26 (3) (May 2022) 309–322, https://doi.org/10.1007/s40291-022-00579-1.
[17] K. Wang, M. Li, H. Hakonarson, ANNOVAR: functional annotation of genetic variants from high-throughput sequencing data, Nucleic Acids Res. 38 (16) (Sep 2010) e164, https://doi.org/10.1093/nar/gkq603.
[18] P. Cingolani, A. Platts, le L. Wang, et al., A program for annotating and predicting the effects of single nucleotide polymorphisms, SnpEff: SNPs in the genome of Drosophila melanogaster strain w1118; iso-2; iso-3, Fly 6 (2) (Apr-Jun 2012) 80–92, https://doi.org/10.4161/fly.19695.
[19] L. Yang, F. Ye, L. Bao, et al., Somatic alterations of TP53, ERBB2, PIK3CA and CCND1 are associated with chemosensitivity for breast cancers, Cancer Sci. 110 (4) (Apr 2019) 1389–1400, https://doi.org/10.1111/cas.13976.
[20] Y. Bao, S. Zhang, X. Zhang, et al., RBM10 loss promotes *EGFR*-driven lung cancer and confers sensitivity to spliceosome inhibition, Cancer Res. 83 (9) (May 2 2023) 1490–1502, https://doi.org/10.1158/0008-5472.CAN-22-1549.
[21] S. Zhang, Y. Bao, X. Shen, et al., RNA binding motif protein 10 suppresses lung cancer progression by controlling alternative splicing of eukaryotic translation initiation factor 4H, EBioMedicine 61 (Nov 2020) 103067, https://doi.org/10.1016/j.ebiom.2020.103067.
[22] D.A. Cross, S.E. Ashton, S. Ghiorghiu, et al., AZD9291, an irreversible *EGFR* TKI, overcomes T790M-mediated resistance to *EGFR* inhibitors in lung cancer, Cancer Discov. 4 (9) (Sep 2014) 1046–1061, https://doi.org/10.1158/2159-8290.CD-14-0337.
[23] Y. Cao, J. Geng, X. Wang, et al., RNA-binding motif protein 10 represses tumor progression through the Wnt/beta- catenin pathway in lung adenocarcinoma, Int. J. Biol. Sci. 18 (1) (2022) 124–139, https://doi.org/10.7150/ijbs.63598.
[24] N. Wu, S. Liu, J. Li, et al., Deep sequencing reveals the genomic characteristics of lung adenocarcinoma presenting as ground-glass nodules (GGNs), Transl. Lung Cancer Res. 10 (3) (Mar 2021) 1239–1255, https://doi.org/10.21037/tlcr-20-1086.