



Mutually Exclusive TP53 and RBM10 Alterations Define Distinct Genomic Contexts in EGFR-Mutant Early-Stage NSCLC

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INTRODUCTION

EGFR-mutant lung adenocarcinoma (LUAD) is biologically heterogeneous. Although TP53 is a common co-mutation associated with aggressive tumor behavior, the genomic and tumor microenvironmental context of other recurrent alterations, including RBM10, remains incompletely understood. We investigated whether RBM10- and TP53-co-mutated EGFR-positive tumors represent distinct clinicogenomic subgroups and explored their tumor immune microenvironment (TIME) phenotypes using GigaTIME¹, a deep learning model that infers multiplex protein signals from routine H&E whole-slide images (WSIs).

DISCUSSION AND CONCLUSION

Conclusion

- Mutually exclusive RBM10 and TP53 alterations define distinct clinicogenomic subgroups of EGFR-mutant LUAD.
- RBM10-mutant tumors show earlier-stage disease, L858R enrichment, lower mutation counts, and a less inflamed, less stromally activated microenvironment.

Take Away Message

- **RBM10 and TP53 co-mutations may represent distinct biological trajectories within EGFR-mutant LUAD.**

RESULTS

RBM10 and TP53 alterations were strongly mutually exclusive

Among 365 EGFR-mutant tumors, 91% were stage I–II. TP53 mutations were identified in 93 cases and RBM10 mutations in 89 cases. Only three tumors harbored both alterations, indicating strong mutual exclusivity(OR=0.08, P=5.8×10^{−9}). The demographic distribution were summarized in table 1.

RBM10- and TP53-mutant tumors had distinct clinicogenomic features

Compared with EGFR/TP53-mutant tumors, EGFR/RBM10-mutant tumors were associated with:

- Earlier-stage disease, Tis/IA: 88% vs. 60%
- Older age, median: 66 vs. 62 years; *P*=0.018
- Higher prevalence of EGFR L858R: 81% vs. 40%; *P*<0.001
- Lower tumor mutation counts: *P*=1.03×10^{−5}

No significant differences in fitted COSMIC mutational signature exposures were observed between the two groups.

Table 1. Clinicopathological characteristics of EGFR-mutant NSCLC stratified by TP53 and RBM10 co-mutation status

	EGFR mutated, n=365	EGFR co-mutation status		p value
		TP53 , n=90	RBM10, n=86	
Age(range)	65 (32.0-88.0)	62.5 (38.0-87.0)	66.5 (43.0-88.0)	0.018
Sex				
Male	124 (34%)	33 (37%)	54 (37%)	1.000
Female	241 (66%)	57 (63%)	32 (63%)	
Tabacco use history				0.801
Never	288 (79%)	67 (74%)	67 (78%)	
Current or Previous	77 (21%)	23 (26%)	19 (22%)	
Family history of lung cancer				0.217
Absent	297 (81%)	79 (88%)	69 (80%)	
Presence	68 (19%)	11 (12%)	17 (20%)	
Stage (AJCC 8th)				<0.001
Tis	67 (18%)	3 (3%)	19 (22%)	
IA	225 (62%)	51 (57%)	57 (66%)	
IB	27 (7%)	9 (10%)	5 (6%)	
II	15 (4%)	7 (8%)	4 (5%)	
III	22 (6%)	13 (14%)	1 (1%)	
IV	2 (1%)	7 (8%)	0 (0%)	
Histology				0.614
Adnocarcinoma	359 (98%)	89 (99%)	84 (98%)	
Squamous cell carcinoma	1 (0%)	0 (0%)	0 (0%)	
Adenosquamous carcinoma	5 (1%)	1 (1%)	2 (2%)	
WHO grading of adenocarcinoma				<0.001
grade 1	216 (59%)	27 (30%)	62 (72%)	
grade 2	56 (15%)	15 (17%)	12 (14%)	
grade 3	87 (24%)	46 (51%)	10 (12%)	
NA	6 (2%)	2 (2%)	2 (2%)	
EGFR status				<0.001
L858R	200 (55%)	42 (47%)	70 (81%)	
Exon19del	125 (34%)	38 (42%)	12 (14%)	
Others*	40 (11%)	10 (11%)	4 (5%)	

Data are median (minimum-maximum) or n(%). EGFR, Epidermal growth factor receptor; *Others include: G719X, S768I, E709A, etc.

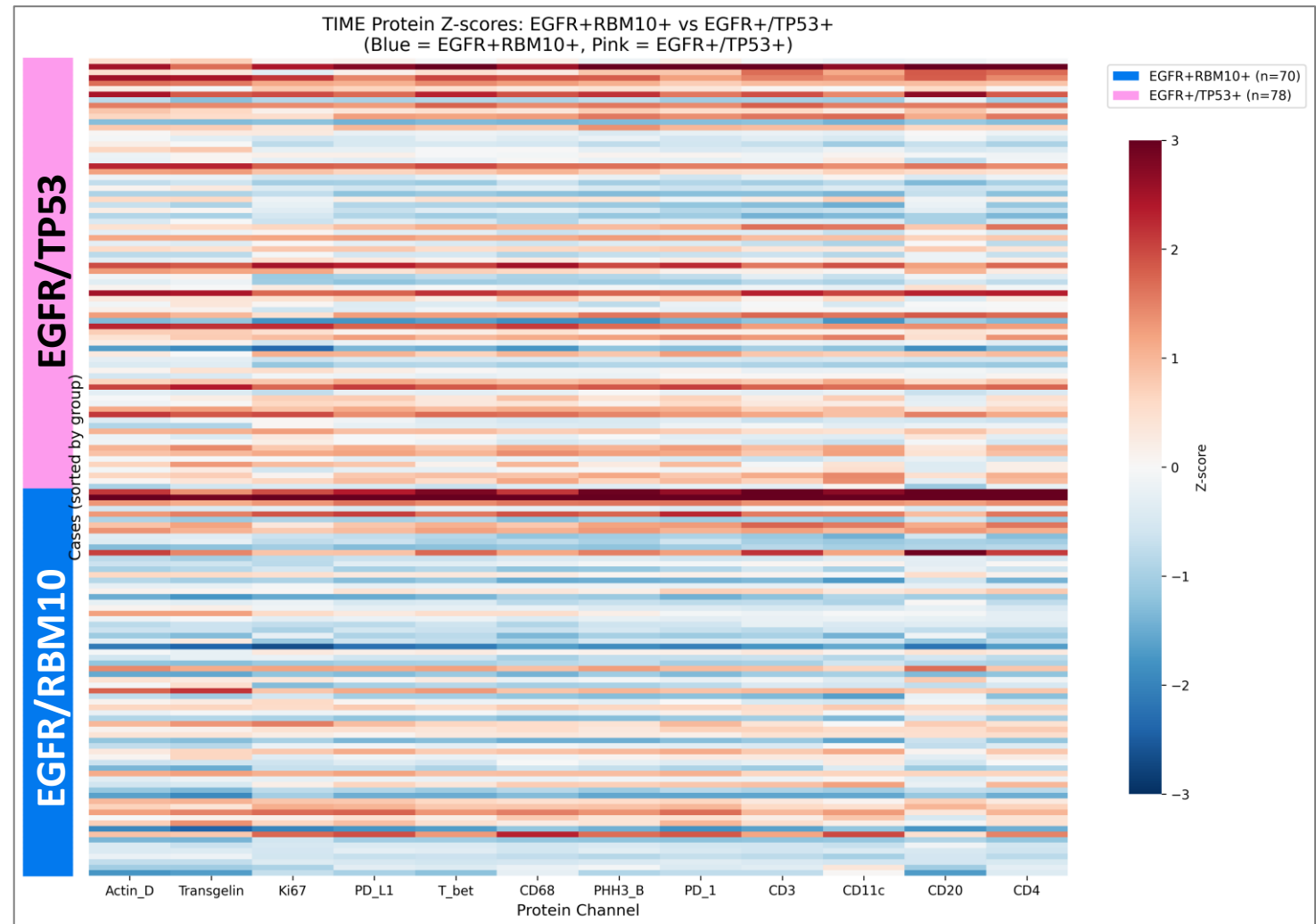


Figure 2. Heatmap of GigaTIME-derived virtual protein signal z-scores comparing EGFR/RBM10- and EGFR/TP53-mutant tumors.

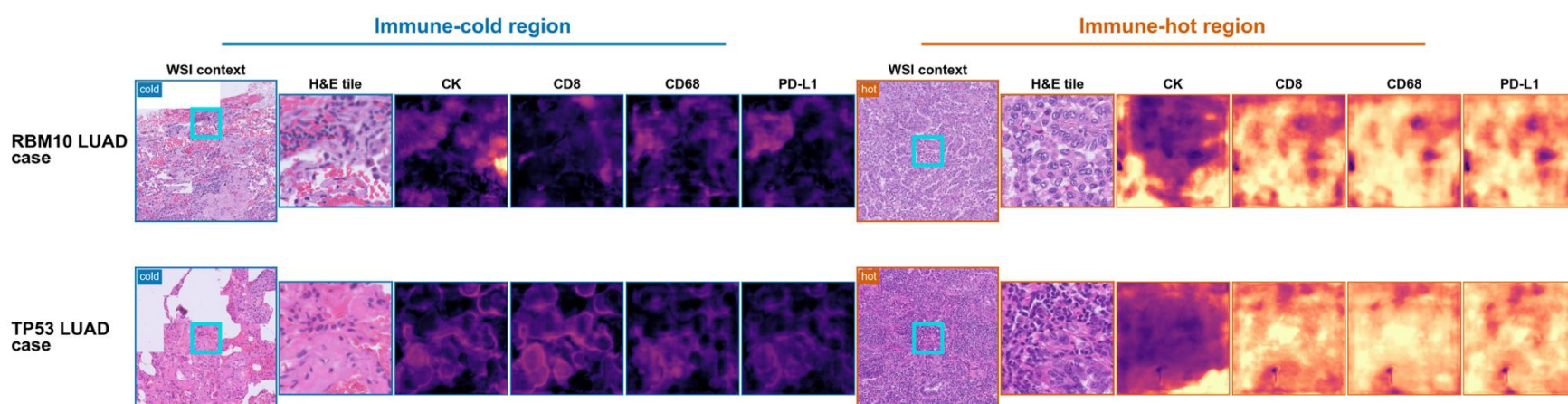
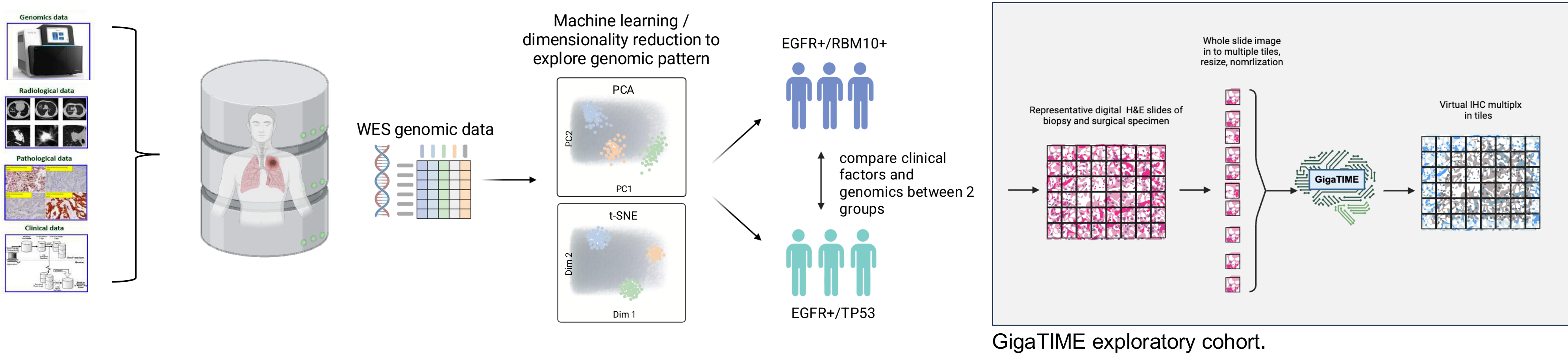


Figure 3. Representative cases demonstrating GigaTIME-derived virtual protein images.

METHODS

Study cohort and genomic analysis

We analyzed 365 EGFR-mutant LUAD cases from the Taipei Veterans General Hospital (TVGH) NSCLC multi-omic databank (NSTC 114-2321-B-075-007). Somatic variants classified by Variant Effect Predictor as having moderate or high functional impact were used to construct a mutation matrix. Genomic patterns were explored using principal component analysis and t-distributed stochastic neighbor embedding. Co-mutation relationships were assessed using Fisher's exact test, and clinicopathological characteristics were compared between genomic subgroups. Tumor mutation counts and COSMIC mutational signatures² were also compared between EGFR/RBM10- and EGFR/TP53-mutant tumors.



Exploratory GigaTIME analysis

Among cases with available WSIs, two mutually exclusive subgroups were selected: EGFR/RBM10-mutant, TP53-wild-type: *n*=70: EGFR/TP53-mutant, RBM10-wild-type: *n*=78 WSIs were processed using GigaTIME to generate z-score-normalized virtual protein signals across 20 biological channels. Technical channels—DAPI, TRITC, and Cy5—were excluded. Protein channels were aggregated into six biologically defined composite categories: 1)T-cell ; 2) Myeloid; 3) B-cell/Plasma; 4) CAF/Stromal; 5) Checkpoint; 6)Tumor/Epithelial. Differences between groups were quantified using Hedges' *g*, with false discovery rate correction for multiple comparisons.

REFERENCES & ACKNOWLEDGEMENTS

1. Valanarasu JMI, Xu H, Usuyama N, et al. Multimodal AI generates virtual population for tumor microenvironment modeling. *Cell*. 2026;189(2):386-400.e19. doi:10.1016/j.cell.2025.11.016
2. Sondka Z, Dhir NB, Carvalho-Silva Dmed M, et al. COSMIC: a curated database of somatic variants and clinical data for cancer. *Nucleic Acids Res*. 2024 Jan 5;52(D1):D1210-D1217. doi: 10.1093/nar/gkad986. PMID: 38183204; PMCID: PMC10767972.

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