SETD2 a potential tissue-agnostic predictive biomarker for ICIs in solid tumors

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Background

In the past decade immune-checkpoint inhibitors (ICIs) has revolutionized the treatment of patients with multiple types of cancer, but the predictive biomarkers are limited. SETD2 is an essential gene related to DNA damage repair(DDR) and an IFN-α induced immune response, indicating a predictive role in immunotherapeutic efficacy.

Methods

In our discovery cohort, we reviewed 6726 sequencing samples, among them 375 samples were detected with SETD2 mutation and 13 patients from 9 centers were ICIs treated. Validation cohort datas included the TCGA, the MSKCC and the POPLAR/OAK cohort and 10 public ICIs treated cohorts. PolyPhen-2 and SIFT were used to distinguish deleterious mutations from tolerated mutations. Comparisons of tumor mutation burden (TMB), MSIsensor, survival, immune gene expression were calculated.

Results

Our discovery cohort showed a high ORR for patients with SETD2 mutation which was 53.8% (7/13)for all patients with immunotherapy and 42.9% (3/7) for PD-1/PD-L1 monotherapy.

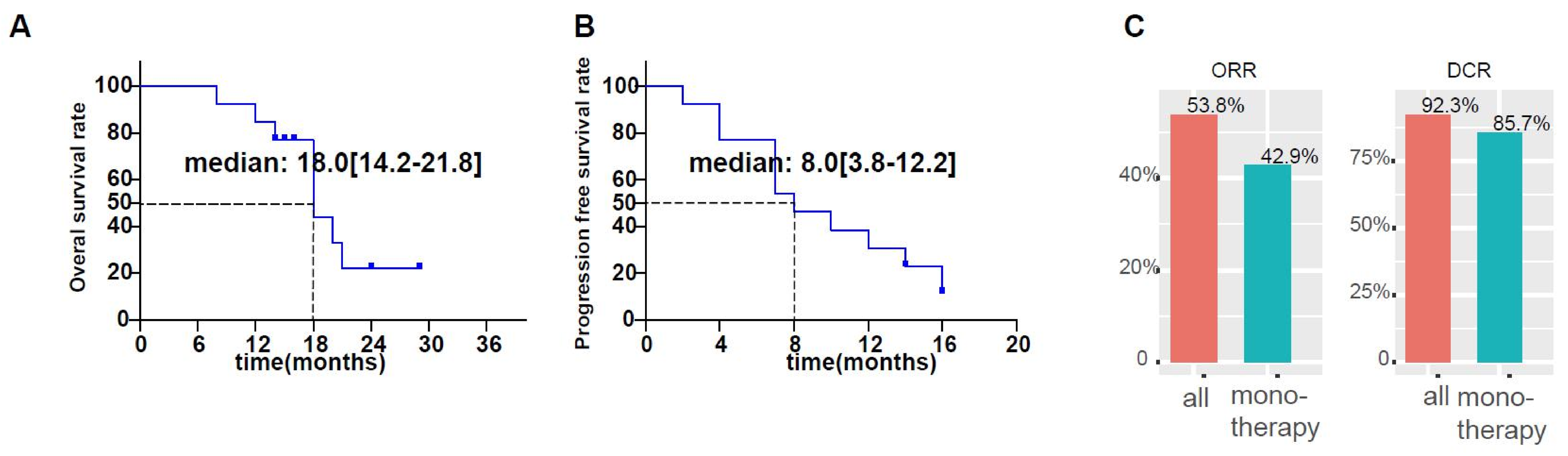

Figure 1: SETD2 deleterious mutations are linked with improved survival outcome in the ICIs treatment cohort.

Results - Continue

A significantly higher TMB was found in SETD2 deleterious mutation group in our discovery cohort including colorectal cancer (p<0.0001), non-small cell lung cancer (p<0.0001), melanoma (p=0.0022) and glioma (p=0.0042).

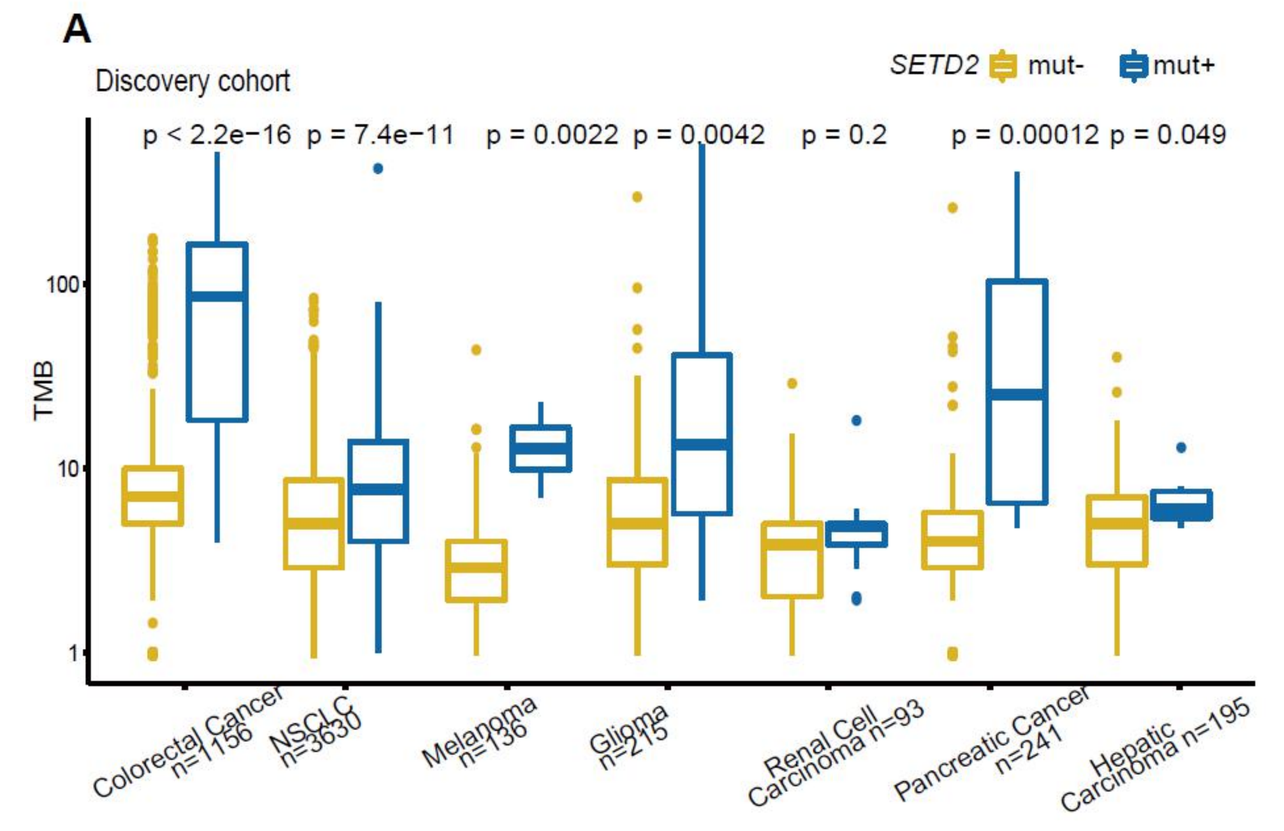

Figure 2 A: SETD2 deleterious mutations are linked with elevated TMB.

SETD2 was associated with higher MSIsensor and was an independent factors influencing MSI-H in gastric adenocarcinoma (p=0.003) and colorectal carcinoma (p<0.0001).

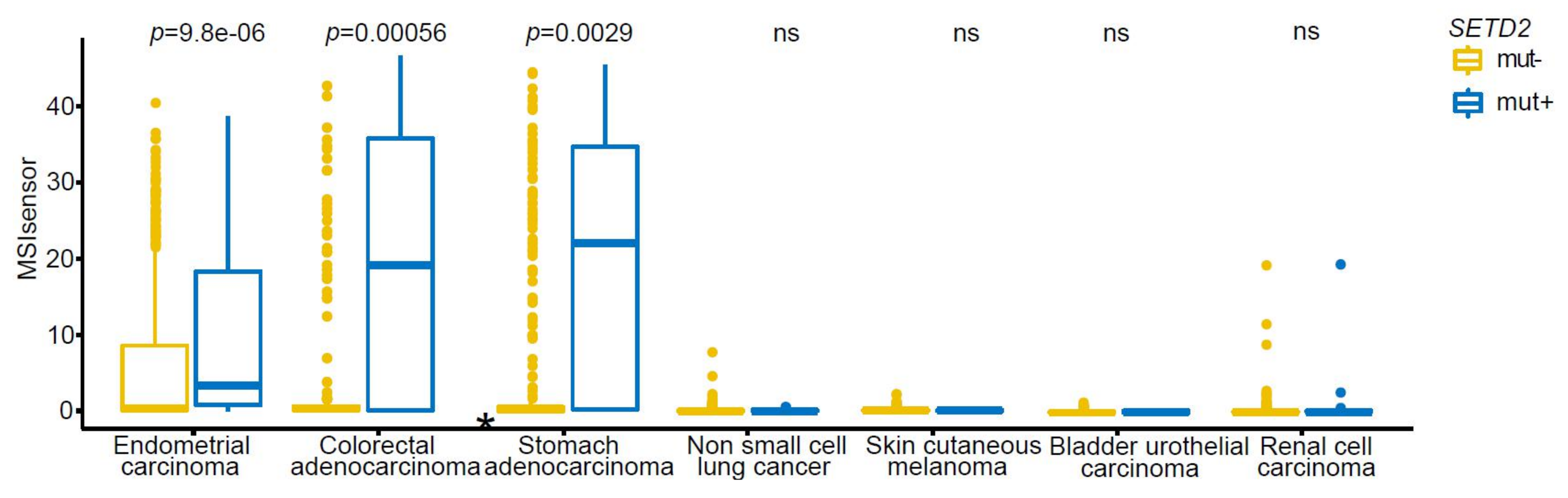

Figure 3 A. The difference of MSIsensor score in patients with SETD2 deleterious mutation and non-deleterious mutation in TCGA cohort across seven cancer types.

Results - Continue

Transcriptomic analysis in seven solid tumors from the TCGA database showed features of inflammated tumor microenvironment in tumors with SETD2 deleterious mutation group especially in renal cell carcinoma, colorectal adenocarcinoma and endometrial carcinoma.

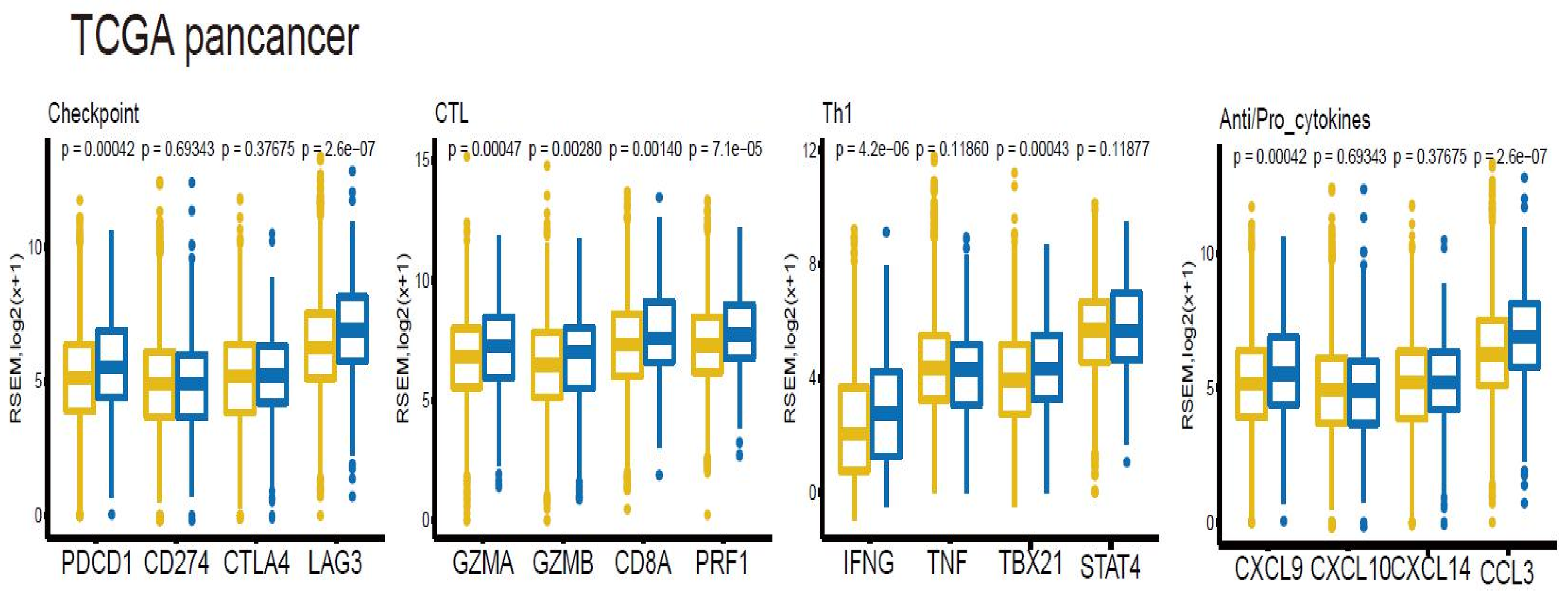

Figure 4 : Comparison of the expression of immune-related gene profiles between SETD2 non-deleterious mutation group and deleterious mutation group in patients in pancancer patient.

Conclusion

We identified a new tissue agnosticpredictive biomarker for ICIs: SETD2 deleterious mutation.