82P: Exploring the prognostic role of DNA damage sensing deficiency for immune checkpoint blockade in diverse cancer types

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BACKGROUND

Immune checkpoint blockade (ICB) produces durable responses on difficult-to-treat tumors, but its effects are heterogeneous on patients. DNA damage response (DDR) is a network of multiple functional pathways to maintain genomic stability, and mutations in DDR genes are a major determinant of response to ICB. However, only a subset of DDR-altered patients benefit from ICB, and their responses vary across cancer types.

METHODS

This is a retrospective pan-cancer study. We assessed the prognostic value of pre-defined core DDR pathways (Ref. 1) in 1,571 patients derived from cBioPortal TMB/Immunotherapy datasets. 7,417 treatment-naïve Chinese patients that underwent targeted next-generation sequencing were then used to compare genomic profiles between DDR proficient and deficient samples. Furthermore, we calculated the tumor-infiltrating lymphocyte (TIL) scores of 3,164 samples derived from TCGA RNAseq datasets to evaluate the tumor microenvironment (TME) with different types of DDR status.

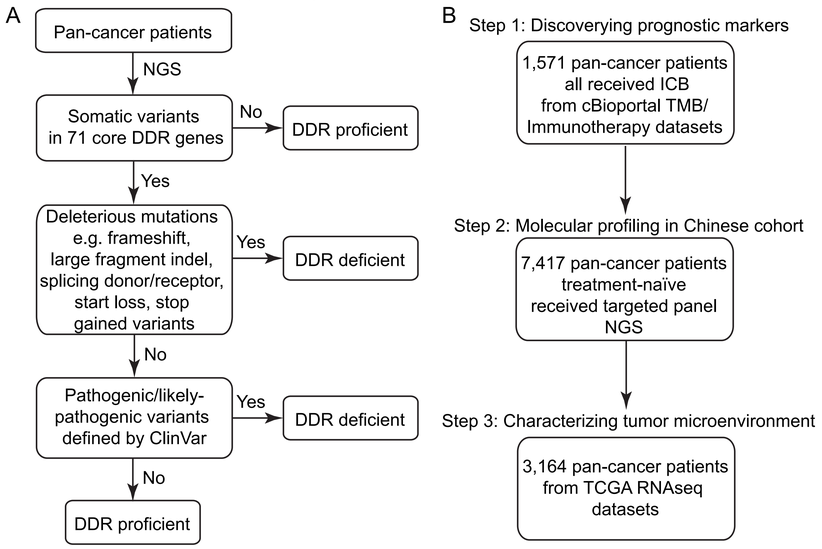

Figure 1. (A) Defination of DDR proficiency and deficiency in this study. (B) The schematics of the study and cohort design.

DISCLOSURE: JY, QO, XC, Xiaoying Wu, Xue Wu, and YS are employees of Nanjing Geneseeq Technology Inc.. All other authors declare no conflict of interest.

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RESULTS

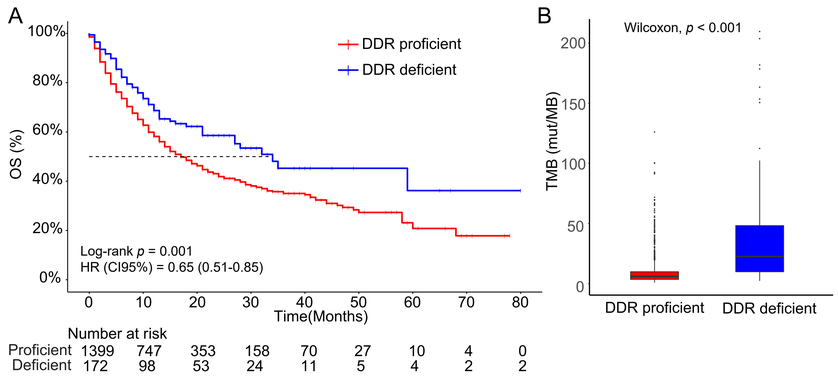

Figure 2. DDR deficient patients (n=172) from the cBioPortal TMB/Immunotherapy datasets showed significantly (A) better ICB overall survival (OS, median OS: 34 vs 17 months) and (B) higher tumor mutation burden (TMB, mean, 9.3 vs 36.1 mut/MB) than DDR proficient patients (n=1,399).

Deficient in DDR pathway	Univariable analysis		Multivariable analysis	
	Hazard ratio (95%CI)	*P* value	Hazard ratio (95%CI)	*P* value
Homologous Recombination	0.652 (0.468-0.907)	**0.010***	0.716 (0.508-1.008)	0.055
Damage Sensing	0.614 (0.412-0.913)	**0.016***	0.661 (0.439-0.995)	**0.047***
Mismatch Repair	0.690 (0.466-1.020)	0.062	0.831 (0.552-1.251)	0.375
Nucleotide Excision Repair	0.690 (0.328-1.450)	0.326	0.818 (0.387-1.729)	0.599
Fanconi Anemia	0.456 (0.064-3.240)	0.421	0.695 (0.098-4.940)	0.716
Base Excision Repair	0.764 (0.191-3.060)	0.702	0.803 (0.200-3.225)	0.757

Table 1. According to the multivariate analysis by the COX regression method, only damage sensing (DS) of the core DDR pathways is an independent prognostic factor for the overall survival of ICB treatment (DS deficient vs proficient: HR, 0.661; 95%CI, 0.439-0.995).

- DS deficient patients showed a significantly longer OS than DS proficient patients (mOS: not reached vs 18 months, $p = 0.02$).

Patient features	DDR proficient (n=6,344)	Non-DS deficient (n=622)	DS deficient (n=451)	P value
Sex				0.188
Female	2,396 (37.8%)	212 (34.1%)	167 (37.0%)	
Male	3,945 (62.2%)	410 (65.9%)	283 (62.7%)	
Age				**0.002****
Mean age in years, (range)	59.6 (15-93)	61.0 (18-98)	60.7 (23-87)	
Type				
Lung Cancer	3,728 (58.8%)	366 (58.8%)	216 (47.9%)	**< 0.001*****
Colorectal Cancer	1,406 (22.2%)	132 (21.2%)	155 (34.4%)	**< 0.001*****
Gastric Cancer	495 (7.8%)	62 (10.0%)	41 (9.1%)	0.118
Hepatobiliary Carcinoma	298 (4.7%)	27 (4.3%)	15 (3.3%)	0.387
Pancreatic Cancer	178 (2.8%)	12 (1.9%)	11 (2.4%)	0.411
Esophagogastric Cancer	96 (1.5%)	10 (1.6%)	10 (2.2%)	0.507
Breast Cancer	143 (2.3%)	13 (2.1%)	3 (0.7%)	0.079

Table 2. Clinical information of the study cohort containing 7,417 treatment-naïve Chinese patients. The majority are DDR proficient patients (85.5%), followed by DDR deficient patients without DS deficiency (non-DS deficient, 8.4%) and DDR deficient patients with DS deficiency (DS deficient, 6.1%).

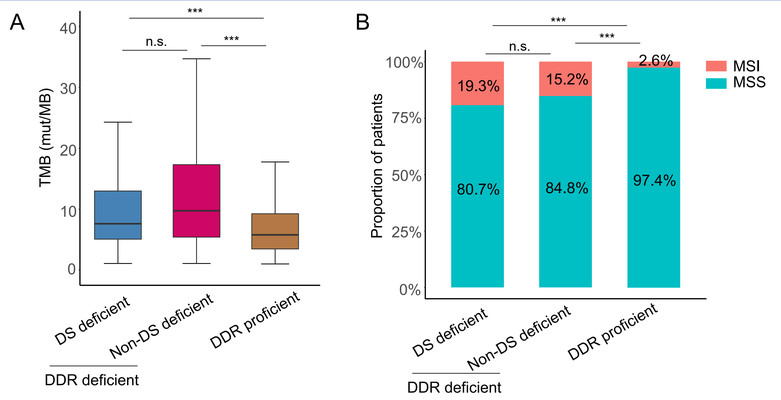

Figure 3. (A) TMB and (B) microsatellite instability (MSI) ratio varied significantly between DDR proficient and deficient subjects in the Chinese cohort, but there is no remarkable difference associated with DS status for DDR deficient patients.

- Compared to non-DS deficient, mutations in *KRAS* and *JAK2* are significantly enriched in DS deficient samples in cBioPortal TMB/Immunotherapy datasets and Chinese cohort ($p < 0.05$).

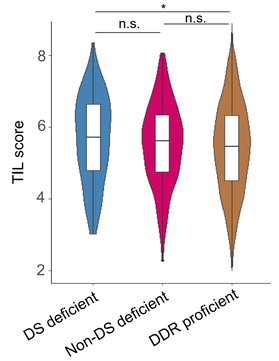

Figure 4. Analysis of the TCGA RNAseq dataset revealed that the total TIL scores of the DS deficient patients, but not the non-DS deficient patients, is significantly higher than that of the DDR proficient subset. The total TIL score calculated by the average of all targeted immune cell scores was directly retrieved from Ref. 2. DS and non-DS deficient are both DDR deficient.

CONCLUSIONS

Damage sensing deficiency is associated with a favorable prognosis of ICB. Molecular profiling reveals unique properties of tumor intrinsic factors in DS deficient cancer patients, which may synergistically modulate lymphocyte infiltration in the TME. The prognostic role of DNA damage sensing may provide insights into biomarker research.

REFERENCES:

1. Knijnenburg TA, et al. Genomic and Molecular Landscape of DNA Damage Repair Deficiency across The Cancer Genome Atlas. Cell reports 2018; 23(1): 239-54 e6.
2. Danaher P, et al. Gene expression markers of Tumor Infiltrating Leukocytes. Journal for immunotherapy of cancer 2017; 5: 18.