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Comprehensive genomic profiling of small bowel adenocarcinoma by tissue and plasma biopsy

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Highlights

- Our research revealed the genomic features of small bowel cancer from both tissue and blood perspectives.
- The relationship between tumor mutational burden (TMB) and other immune characteristics in SBA.
- Plasma biopsy could be a non-invasive alternative for detecting mutations, which is feasible and useful in SBA.
- SBA has a distinct mutation profile from both left-sided and right-sided CRC, but is less different from left-sided.

Abstract

Small bowel adenocarcinoma (SBA) is a rare and aggressive malignancy with limited treatment options and poor prognosis. The molecular landscape and immunological characteristics of SBA are

poorly understood. Here, we performed comprehensive mutation profiling of tissue and plasma biopsies from 143 and 42 patients with SBA. Analysis showed that SBA had a distinct mutation spectrum from left- and right-sided colorectal carcinoma. Plasma biopsy had high concordance with tissue biopsy for single nucleotide variants and structural variants, but low concordance for copy number variations, which showed that plasma biopsy can be an alternative to tissue biopsy. Moreover, we analyzed the association of TMB with clinical and molecular features, and found that TMB was significantly higher in tumors with DNA damage response alterations. Our findings provide valuable insights into the molecular and immunological features of SBA and demonstrate the potential of plasma biopsy as a non-invasive method for SBA diagnosis and treatment.

Previous Next

Keywords

Small bowel adenocarcinoma; Next-generation sequencing; Genomic profiling; Immunological features; Plasma biopsy

Abbreviations

SBA, small bowel adenocarcinoma; CRC, colorectal cancer; NGS, next-generation sequencing; MSI, microsatellite instability; MSS, microsatellite stability; TMB, tumor mutational burden; ctDNA, circulating tumor DNA; cfDNA, cell free DNA; UID, unique identifiers; TPS, tumor proportion score; MTM, Mean tumor molecules

1. Introduction

Small bowel adenocarcinoma (SBA) is a rare and aggressive malignancy that accounts for <1% of all cancer cases worldwide. The incidence of SBA has been increasing over the past decades, reaching an estimated 12,070 new cases and 2070 deaths in the United States in 2023. SBA accounts for 3% of digestive cancers and this proportion increased with an annual percent increase of 5 between 2013 and 2023 [1,2]. The diagnosis and treatment of this disease are challenging, and its etiology, pathogenesis, and molecular features remain poorly understood.

SBA is often asymptomatic or presents with nonspecific symptoms, such as abdominal pain, weight loss, anemia, or obstruction [3]. The diagnosis of SBA is frequently delayed or missed due to the difficulty of accessing and visualizing the small bowel, resulting in more patients presenting with advanced disease. Primary tumor location influences prognosis in small bowel cancer. Duodenal adenocarcinomas, which account for half of all cases, have poorer survival than jejunal (20%) or ileal (15%) adenocarcinomas, according to some studies [4].

The treatment of SBA depends on the stage, location, and histology of the tumor. Surgery is the mainstay of treatment for localized disease, but about one-third of cases are inoperable [5]. Adjuvant chemotherapy or chemoradiotherapy may improve survival in some postoperative patients with high-risk features [6]. For advanced or metastatic disease, systemic therapy is the only option, but the efficacy is limited and the optimal regimen is unclear [7]. In the past decades, the treatments of SBA were referred to colorectal cancer (CRC). However, many evidences have suggested that therapies for CRC are not suitable for SBA. For instance, trials have shown that, unlike CRC patients, SBA patients with wild-type *RAS* do not benefit from cetuximab and panitumumab [8]. Moreover, there was no sufficient evidence to support that anti-EGFR therapy and regorafenib can be subsequent therapy used for SBA metastatic patients, as in CRC patients [9].

The molecular landscape of SBA has been explored by several studies using next-generation sequencing (NGS) techniques [10,11]. The most frequent genomic alteration in SBA *was* KRAS*, TP53, PIK3CA,APC, SMAD4*. And some studies have revealed that SBA shares some common mutations with CRC, such as *KRAS*, *TP53*, and *SMAD4* [[10], [11], [12]]. However, SBA also has distinct features that differentiate it from CRC, such as the low frequency of *APC* mutation and *BRAF* V600E mutation [13]. Importantly, microsatellite instability-high/deficient mismatch repair (MSI-H/dMMR), programmed death-ligand 1 (PD-L1) expression, and tumor mutational burden-high (TMB-H) are enhanced in SBA compared to CRC, which may have implications for immunotherapy [14,15]. Moreover, SBA exhibits a high degree of heterogeneity and complexity at the genomic level.

Most of the previous studies on SBA used tissue biopsies as the source of DNA for mutation profiling. However, tissue biopsies are invasive and difficult to access in the metastatic setting and may not reflect the spatial and temporal heterogeneity of tumors [[16], [17], [18]]. Liquid biopsy is a non-invasive alternative that can capture circulating tumor DNA (ctDNA) from blood samples [19,20], which has been shown to be feasible and useful for detecting mutations in various cancers [21,22], but its application in SBA is limited.

In this study, we performed comprehensive mutation profiling of tissue and plasma biopsies from patients with SBA using NGS techniques. We identified several key molecular features of this disease and compared the mutation spectrum in SBA with left-sided and right-sided CRC. The concordance and discordance of tissue and plasma biopsies were evaluated to explore the feasibility of replacing tissue biopsy with plasma biopsy. And the association of TMB with clinical and molecular features was also analyzed. Our findings provide novel insights into the genomic landscape and immunological characteristics of SBA, which may have implications for diagnosis, prognosis, and treatment.

2. Materials and methods

2.1. Patients and samples

We retrospectively analyzed 179 patients with small bowel adenocarcinoma (143 tumor sequencing and 42 plasma sequencing) enrolled between July 2017 and May 2023, of whom 6 patients had matched tissue and blood samples collected no >2 months apart. The blood sampling occurred after postoperative recurrence or progression, specifically at least one month after chemotherapy. Clinical information including demographics and pathologic diagnoses was collected. The diagnosis of tumor location is determined by the patient's surgical history and comprehensive evaluation based on imaging examination, pathological evaluation, physical examination, and medical history. To compare SBA with different-sided CRCs, 148 patients with left-sided colorectal carcinoma and 147 patients with right-sided colorectal carcinoma were also enrolled between April 2017 and June 2023. All procedures were conducted in accordance with the Declaration of Helsinki. The study was approved by the ethics committee of The Second Xiangya Hospital of Central South University (No. 2023–135-002). Informed consent was obtained from all participants for mutational analysis.

2.2. Sample processing and DNA extraction

A total of 10 mL peripheral blood samples were collected in Streck tubes. Within 3 days, the sample was separated by centrifugation at 1600×*g* for 10 min, and the supernatant was transferred to microcentrifuge tubes, centrifuged again at 16,000×*g* for 10 min to remove cell debris, and then frozen at −80 °C. Circulating cell free DNA (cfDNA) was extracted from 4 to 5 mL (median, 4 mL) of plasma using the QIAamp Circulating Nucleic Acid Kit (Qiagen). The concentration and fragment length of cfDNA were determined using an Agilent 2100 Bioanalyzer (Agilent Technologies, Inc.).

Tumor DNA was extracted from fresh frozen tissues or formalin-fixed, paraffin-embedded (FFPE) tumor tissue specimens using the QIAamp DNA Mini Kit (Qiagen) and ReliaPrep FFPE gDNA Miniprep System (Promega), respectively. Germline genomic DNA was isolated from peripheral blood lymphocytes (PBL) using the QIAamp DNA Blood Mini Kit (Qiagen).

2.3. Library construction and next generation sequencing (NGS)

For germline genomic DNA and tumor DNA, 300 to 800 ng DNA was sheared into fragments at a 200 to 250 bp peak with a Covaris S2 ultrasonicator (Covaris, Inc), and indexed NGS libraries were prepared using NEBNext Ultra DNA Library Prep Kit for Illumina (NEB). cfDNA (median, 50 ng; range 16–111 ng) was used for library construction, and unique identifiers (UID) were tagged on each double-stranded DNA to distinguish authentic somatic mutations from artifacts, improving the ability to precisely track individual plasma molecules.

DNA libraries were hybridized with custom-designed cancer-related gene panels (spanning from 810 to 1021 genes), of which 1021-gene panel constituted 88%. The hybridized libraries were sequenced using a 100-bp paired-end configuration on a DNBSEQ-T7RS sequencer (MGI Tech, Beijing, China).

The median value of effective depth of coverage was 1700× (range, 480–3700×) in tissue and 5600× (range, 2300-12,000×) in plasma samples. Clean reads after adaptor sequences and low-quality

reads removal were aligned to the reference human genome (hg19) by Burrows-Wheeler Aligner (BWA, version 0.7.12-r1039). Duplicated reads were marked and removed using MarkDuplicates tool in Picard (version 4.0.4.0; Broad Institute) for tumor and germline genomic DNA. For cfDNA, duplicated reads were identified by UID and the position of template fragments to eliminate errors introduced sequencing using realSeq (v3.1.0 Geneplus-Beijing, inhouse). Realignment and recalibration were performed using GATK (version 3.4 46-gbc02625). Single nucleotide variants (SNVs), small insertions and deletions (Indels) and copy number variants (CNVs), and structural variants (SVs) were identified by TNscope, GATK, CNVKit and NCsv2 respectively.

2.4. ctDNA detection

After sequencing errors were polished by UID, SNV calling was performed using a custom bioinformatics pipeline optimized for ultra-low-frequency mutation calling. SNV and indel calling were carried out mainly by realDcaller, while TNscope (Sentieon Inc.) was used as auxiliary software to improve the detection of long indels. Upon annotation completion, variants were filtered according to the following criteria: (i) the variants present in matched genomic DNA were removed; (ii) the single-nucleotide polymorphisms at >1% population allele frequency in ExAc or 1000 Genomes Project were filtered; (iii) the variant positional depth was at least >300 ×; and (iv) for background error removal, a set of ~500 healthy individual plasma samples were sequenced to construct a background estimate VAF distribution model for each target SNV.

cfDNA variants were considered to be true somatic mutations, if the following stringent conditions were met: (i) for hotspot mutations, ≥4 high-quality support reads, or for non-hotspots, at least ≥8 support reads; and (ii) clonal hematopoiesis were filtered through deep sequencing of paired white blood.

Tumor somatic copy number variants were identified with CNVKit. Copy number (CN) per capture region was calculated from the log2 rate of the detected depth of coverage in tumor samples to the average coverage of ≥50 reference samples without CNV. Copy number ratio was defined as CN/2, and copy number ratios <0.7 or >1.3 were counted as deleted or amplified, respectively. And CNV calls were typically reviewed by a professional to ensure their accuracy and reliability.

2.5. Assessment of TMB, TPS and MSI status

TMB was defined as the number of somatic SNVs and indels per megabyte bases in coding regions detected in tumor tissues and plasma samples and categorized into high-TMB and low-TMB. TMB in the top quartile (>25%) was considered as high-TMB. PD-L1 staining was assessed through immunohistochemistry using the 22C3 PharmDx assay (Dako North America). PD-L1 tumor proportion score (TPS) was estimated as the percentage of tumor cells for membranous PD-L1 staining for each section. The MSI status was inferred using the MSIsensor (v0.5) software [23]. It computes length distributions of microsatellites per site in paired tumor and normal sequence data, subsequently using these to statistically compare observed distributions in both samples. And MSI-

high (MSI-H) was defined on an empirically defined cut-off of MSI score>8%. Considering the impact of tumor cell fraction on MSI status evaluation, the tumor was considered as MSI-unknown (MSI-U) if the maximum somatic allele frequency (MSAF) was lower than 0.05.

2.6. Statistical analysis

Differences in variables between tissue and plasma cohorts were assessed using Mann-Whitney test for continuous variables and Fisher's exac*t*-test or Chi-square test for categorical variables. The concordance of genomic alterations between tissue and plasma biopsies was assessed by Cohen's kappa coefficient. The association of TMB with clinical and molecular features was evaluated by Mann-Whitney *U* test or Spearman's rank correlation coefficient. The Benjamini-Hochberg (BH) method was used to correct the *p*-values for multiple comparisons. All statistical analyses were performed using R software version 4.2.3. A two-sided *P* value <0.05 was considered statistically significant.

3. Result

3.1. Study design and patient demographics

Tissue biopsies were obtained from 143 patients, and plasma biopsies were obtained from 42 patients, including 6 patients with matched samples. They were assigned to two cohorts: tissue cohort (with tissue biopsy) and plasma cohort (with plasma biopsy). The demographics and clinical features were balanced in these cohorts, with no significant difference observed except clinical stage (Table 1). The median age at diagnosis was 59years (range, 28–83) for tissue cohort and 58years (range, 31–76) for biopsy cohort. They had duodenal tumors in 89.2% and 92.7% of cases, respectively. Among those with available clinical information, approximately 50% had stage IV cancer, and the plasma group had more stage IV cancer (45.5% versus 78.8%, *P*=0.0014). This is in line with our expectations, stage IV patients tended to have more blood sampled. Liver metastasis was present in 31 (56.4%) and 18 (69.2%) of the stage IV patients in each cohort. In addition, nearly 5.0% patients had MSI-H and median TMB was 5 mutations per megabase. No significant difference was observed in MSI status or TMB between two cohorts.

Table 1. Cinical characteristics of SBAs in tissue and plasma cohorts.

	Small bowel adenocarcinoma		
Characteristic	**tissue biopsy**	**plasma biopsy**	**P.value**
	***n*=143**	***n*=42**	
Age, years			0.1622
Median	59	58	

Small bowel adenocarcinoma					
Characteristic	**tissue biopsy**		**plasma biopsy**		**P.value**
	***n*=143**		***n*=42**		
Range	28–83		31–76		
Unknown - no.	1		0		
Gender - no. (%)					1
Male	81	(56.6%)	24	(57.1%)	
Female	62	(43.4%)	18	(42.9%)	
Location - no.					0.6540
Duodenum	107	(89.2%)	38	(92.7%)	
Jejunum	8	(6.7%)	1	(2.4%)	
Ilenum	5	(4.2%)	2	(4.9%)	
NA	23		1		
Clinical stage - no. (%)					0.0014
I-III	66	(54.5%)	7	(21.2%)	
IV	55	(45.5%)	26	(78.8%)	
NA	22		9		
Metastases - no. (%)					
Liver	31	(56.4%)	17	(65.4%)	0.4405
Lung	11	(20.0%)	3	(11.5%)	0.5308
Peritoneum	11	(20.0%)	5	(19.2%)	1
MSI - no.(%)					0.6239
MSI-H	7	(5.6%)	2	(9.1%)	
MSS	118	(94.4%)	20	(90.9%)	
NA	18		20		
TMB - muts/Mb					0.3268
mTMB	4.8		5		
Range	0–182.4		0.96–198.72		

Cinical characteristics of SBAs in tissue (n=143) and plasma (n=42) cohorts. The P value is the value of the Fisher test or t-test comparing the clinical characteristics of the two cohorts.

SBA, small bowel adenocarcinoma. MSI-H,microsatellite instability-high. MSS,microsatellite stability. TMB, tumor mutational burden.

For plasma cohort, mean tumor molecules per milliliter (MTM/mL) of plasma was calculated to represent ctDNA level, based on variant allele frequencies and quantity of cfDNA. The formula for calculating MTM/mL is as follows: $MTM/mL = \frac{\text{meanVAF} \times \text{cfDNA mass(ng)} \times 1000\ \text{pg/ng}}{3.3\ \text{pg} \times \text{plasma volume (mL)}}$ [24,25]. The correlations between MTM and clinical parameters were analyzed. Our result showed that MTM correlated with liver metastasis. Patients with liver metastasis had higher MTM than other patients (P=0.0125). And regarding other clinical parameters, no significant difference was observed (Fig. S1 A).

3.2. Small bowel adenocarcinoma mutation profiling

Mutation profiling on tissue and plasma biopsies from two cohorts was performed. We detected 1729 variants in 470 genes from 143 patients in tissue cohort with the detection rate of 100%, comprising 1541 SNVs in 135 (94.4%) patients, 191 CNVs in 49 (34.3%) patients, and 5 SVs in 4 (2.8%) patients. (Fig. 1A). The most frequently mutated genes were *TP53* (58.7%), *KRAS* (43.4%), *SMAD4* (23.8%), and *APC* (20.2%), with *MYC* copy number gain (CNG) being the most common CNV (11.8%) (Fig. 1C).

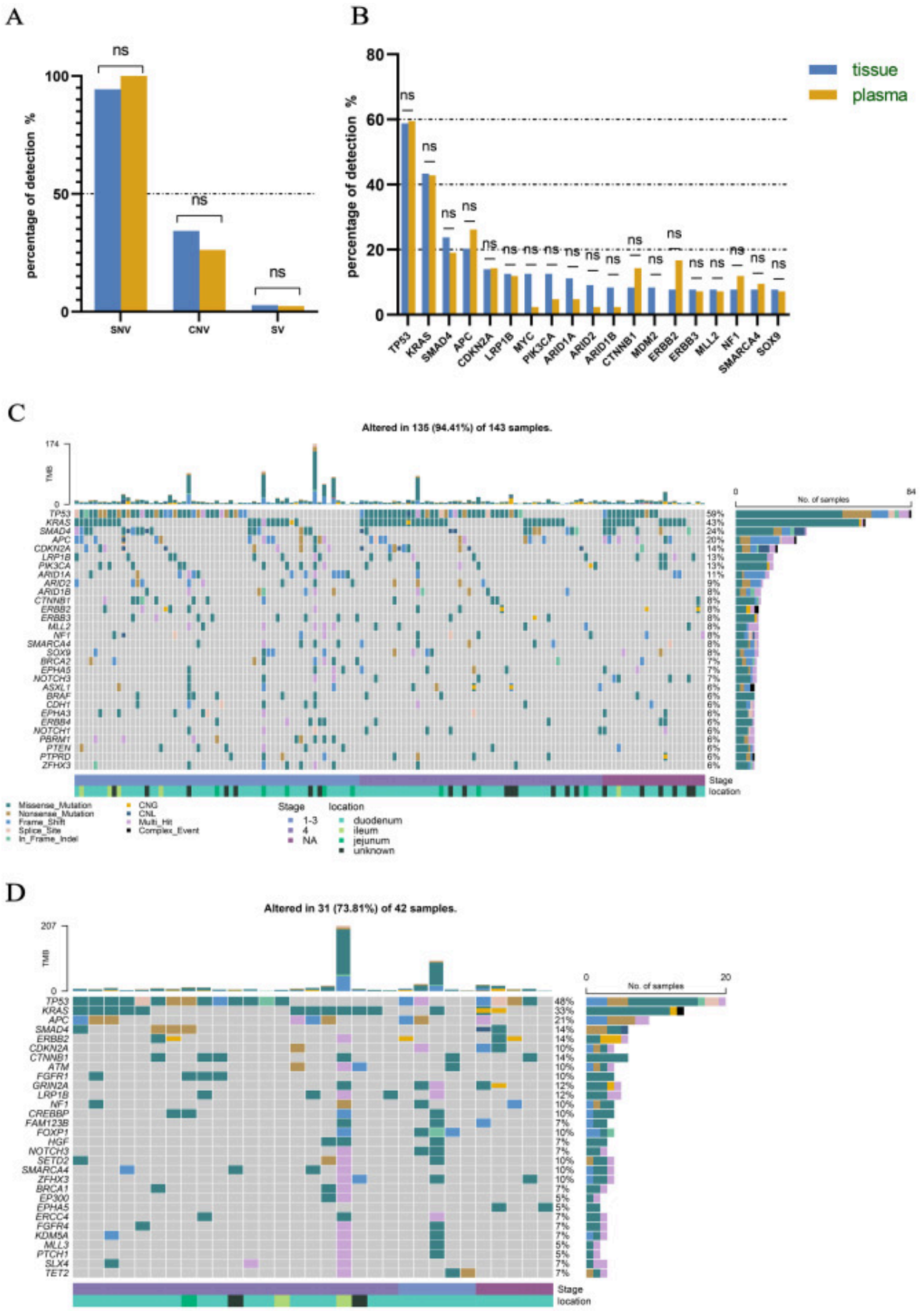

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Fig. 1. Frequency distribution of alterations in 143 tissue samples and 42 plasma samples of small bowel adenocacinoma. (A)The detection of SNVs, CNVs and SVs in tissue and plasma samples. SNVs, single nucleotide variants. CNVs, copy number variants. SVs, structural variants. (B)The detection of gene alterations in tissue and plasma samples. (C)Genomic profile in tissue samples.Each row represents a gene, and each column represents a patient. The color and shape of the dots indicate the type and frequency of mutations in each gene and patient. The top bar plots show the mutation burden and the bottom bar plots show the clinical information of each patient. The side bar plots show the mutation frequency of each gene. (D)Genomic profile in plasma samples.

A significant difference in KRAS mutation rates between stage IV patients and those in other stages was observed in our study. Among the 121 patients with confirmed TNM staging, 48 (39.7%) had KRAS mutations. Specifically, 28/56 (50.0%) SBA had KRAS mutations, while 20/65 (30.8%) SBA in other stages exhibited KRAS mutations. The KRAS mutation rate was notably higher in stage IV compared to other stages (Fig. S1 B).

In plasma cohort of 42 patients, 601 variants in 265 genes were detected, with the detection rate of 100%, comprising 553 SNVs in 42 (100.0%) patients, 47 CNVs in 11 (26.2%) patients, and 1 SV in 1 (2.4%) patient (Fig. 1A). No significant difference was observed for detection of SNVs, CNVs, and SVs between plasma and tissue samples (Fig. 1A). The four most frequently mutated genes were consistent between plasma and tissue cohorts (Fig. 1D). The detection rate of common mutated genes showed no significant differences between the two cohorts (Fig. 1B). There was a trend towards lower detection rates of *MDM2* (P=0.0711) and *MYC* (P=0.0793) in the plasma cohort, but this was not statistically significant. Most of the identifications in *MDM2* and *MYC* were attributed to copy number variations (CNV), which were poorly detected by plasma biopsy.

3.3. Actionable mutations in small bowel adenocarcinoma

Actionable mutations were defined as gain-of-function or loss-of-function mutations related to the sensitivity or resistance of certain drugs, based on the FDA labeling, National Comprehensive Cancer Network guidelines, expert consensus, and scientific literature. The clinical and experimental evidence is grouped into four levels according to the Standards and Guidelines for the Interpretation and Reporting of Sequence Variants in Cancer issued by AMP/ASCO/CAP [26]. The evidence of major actionable mutations was level C in our study. More details of actionable alterations were available (Table S2). In the tissue cohort, we identified 274 actionable mutations in 59 genes, affecting 114 (79.7%) patients. These comprised 192 actionable SNVs in 103 (72.0%) patients, 79 actionable CNVs in 37 (25.9%) patients, and 3 actionable SVs in 3 (2.1%) patients (Fig. 2A). The most frequently altered genes with actionable implications were *KRAS* (42.0%), *PIK3CA* (11.8%), and *CDKN2A* (11.8%) (Fig. 2C). Among the 59 actionable *KRAS* SNVs, most (72.8%) were in exon 2 and codon 12, with G12D (17/59, 28.8%) and G12V (17/59, 28.8%) being the predominant variants. These were followed by G13D (7/59, 11.8%) and G12R (6/59, 10.2%), while G12C mutation was not detected.

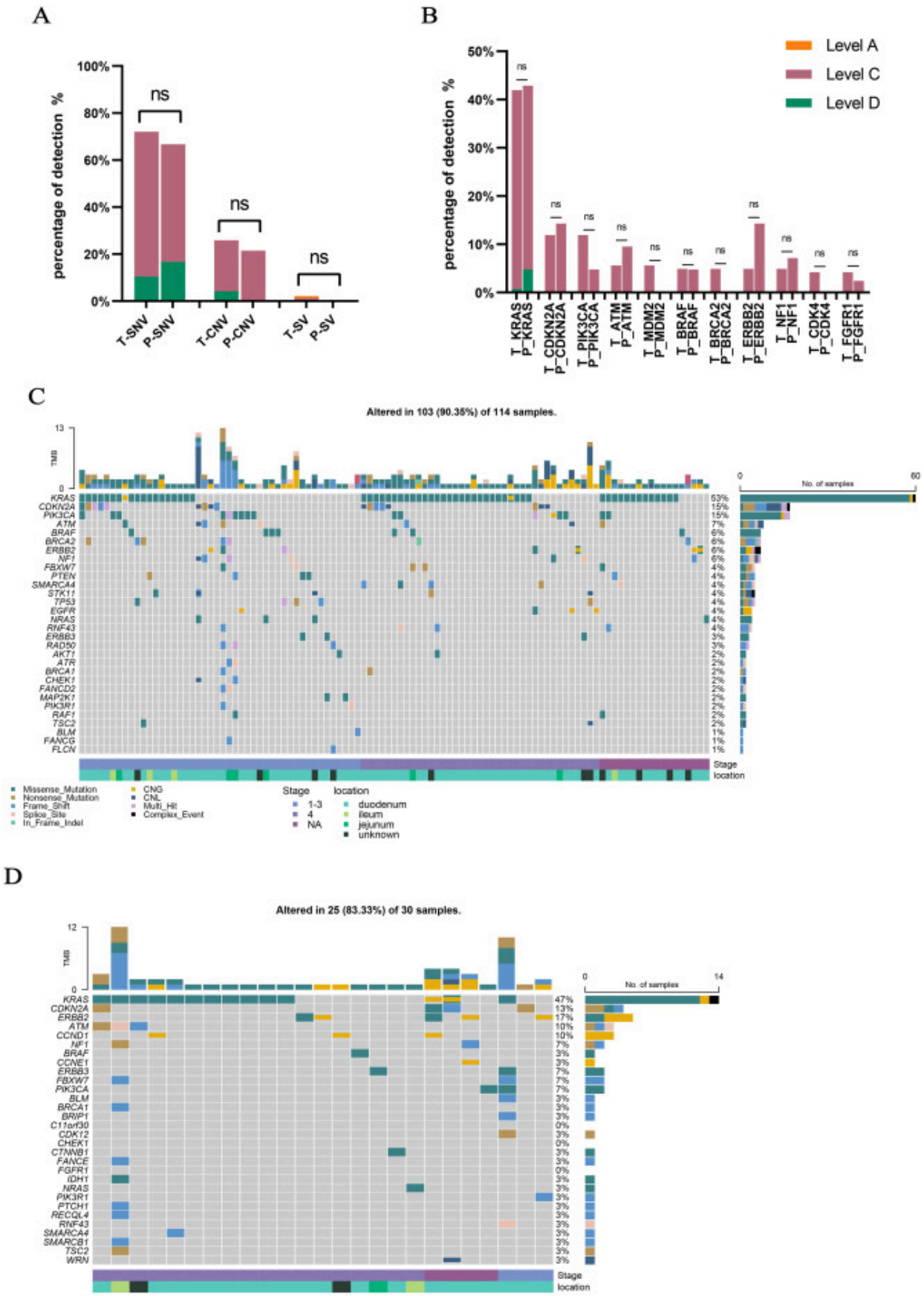

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Fig. 2. Frequency distribution of actionable alterations in 143 tissue samples and 42 plasma samples of small bowel adenocacinoma. (A)The detection of actionable SNVs, CNVs and SVs in tissue and plasma samples. SNVs, single nucleotide variants. CNVs, copy number variants. SVs, structural variants.The color indicate the evidence level of alteration. Level A, biomarkers that predict response or resistance to US FDA-approved therapies for a specific type of tumor or have been included in professional guidelines as therapeutic, diagnostic, and/or prognostic biomarkers for specific types of tumors; Level B, biomarkers that predict response or resistance to a therapy based on well-powered studies with consensus from experts in the field, or have diagnostic and/or prognostic significance of certain diseases based on well powered studies with expert consensus; Level C, biomarkers that predict response or resistance to therapies approved by FDA or professional societies for a different tumor type (ie, off-label use of a drug), serve as inclusion criteria for clinical trials, or have diagnostic and/or prognostic significance based on the results of multiple small studies; Level D, biomarkers that show plausible therapeutic significance based on preclinical studies, or may assist disease diagnosis and/or prognosis themselves or along with other biomarkers based on small studies or multiple case reports with no consensus. (B)The detection of actionable gene alterations in tissue and plasma samples. (C-D)Genomic profiles of actionable alterations in tissue and plasma samples.

In plasma cohort, we identified 74 actionable mutations in 30 genes, affecting 30 (71.4%) patients. These comprised 56 actionable SNVs in 28 (66.7%) patients and 18 actionable CNVs in 9 (21.4%) patients (Fig. 2A). No significant differences were observed in the altered genes with actionable implications between tissue and plasma cohorts (Fig. 2B,D). The detection of *KRAS* mutations was similar to that in the tissue cohort. Of the 16 actionable SNVs, G12D (6/16, 37.5%) and G12V (5/16, 31.2%) mutations were the dominant variants. And there was no evidence of G12C mutation either.

3.4. Signaling pathway mutations in tissue and plasma samples

Signaling pathways based on the mutation data from tissue biopsies of 143 patients were analyzed. Ten classic signaling pathways were investigated, including Cell Cycle, HIPPO, MYC, NOTCH, NRF2, PI3K, TGF-β, RTK RAS, TP53, and WNT [27]. We identified 750 (43.4%) pathway mutations in 141 (98.6%) patients, involving 638 SNVs in 135 (94.4%) patients, 108 CNVs in 43 (30.1%) patients, and 4 SVs in 3 (2.1%) patients. The most frequently altered pathways were RTK RAS (119 pts., 83.2%), TP53 (105 pts., 73.4%) and WNT (51 pts., 35.7%) (Fig. 3).

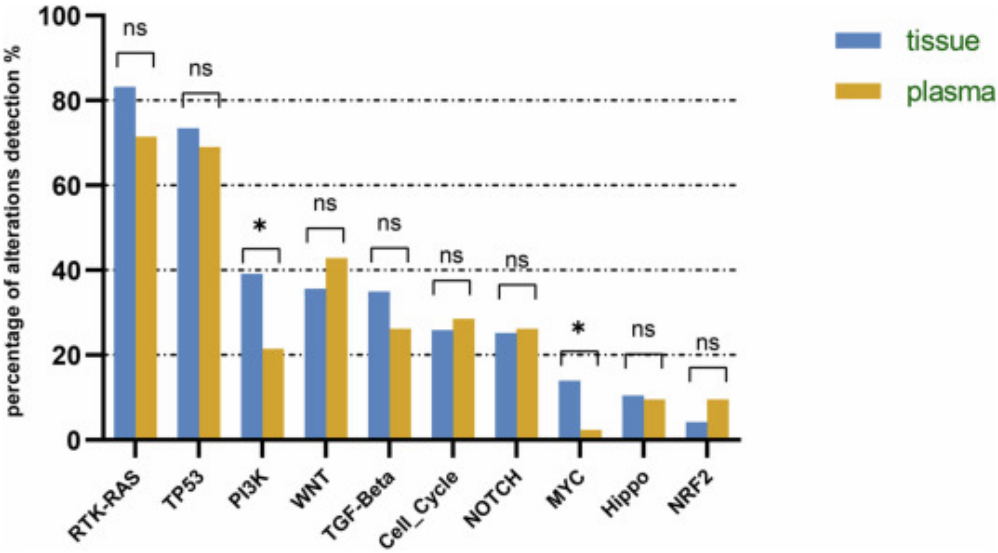

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Fig. 3. The detection of signal pathways variants in tissue and plasma samples.

In plasma cohort, 225 (37.4%) pathway variants were identified in 36 (85.7%) patients, comprising 225 SNVs in 36 (85.7%) patients and 22 CNVs in 10 (23.8%) patients. The most frequently altered pathway was RTK RAS (30 pts., 71.4%) which same as tissue cohort, followed by TP53 (29 pts., 69.0%) and WNT(18 pts., 42.8%). Compared with tissue cohort, the frequency of MYC altered pathway was extremely lower in plasma cohort (14.0% versus 2.4%, P=0.0494) (Fig. 3).

3.5. Analysis of immunological characteristics

The association of TMB, a biomarker of immunotherapy efficacy, with clinical and molecular features was examined in SBA. The median TMB in tissue samples was 4.8 mutations per megabase (muts/Mb; range, 0–182.4), whereas the median TMB in plasma samples was 5 muts/Mb (range, 0–198.7). The frequency distribution of TMB in tissue and plasma samples was similar (Fig. 4A, B).

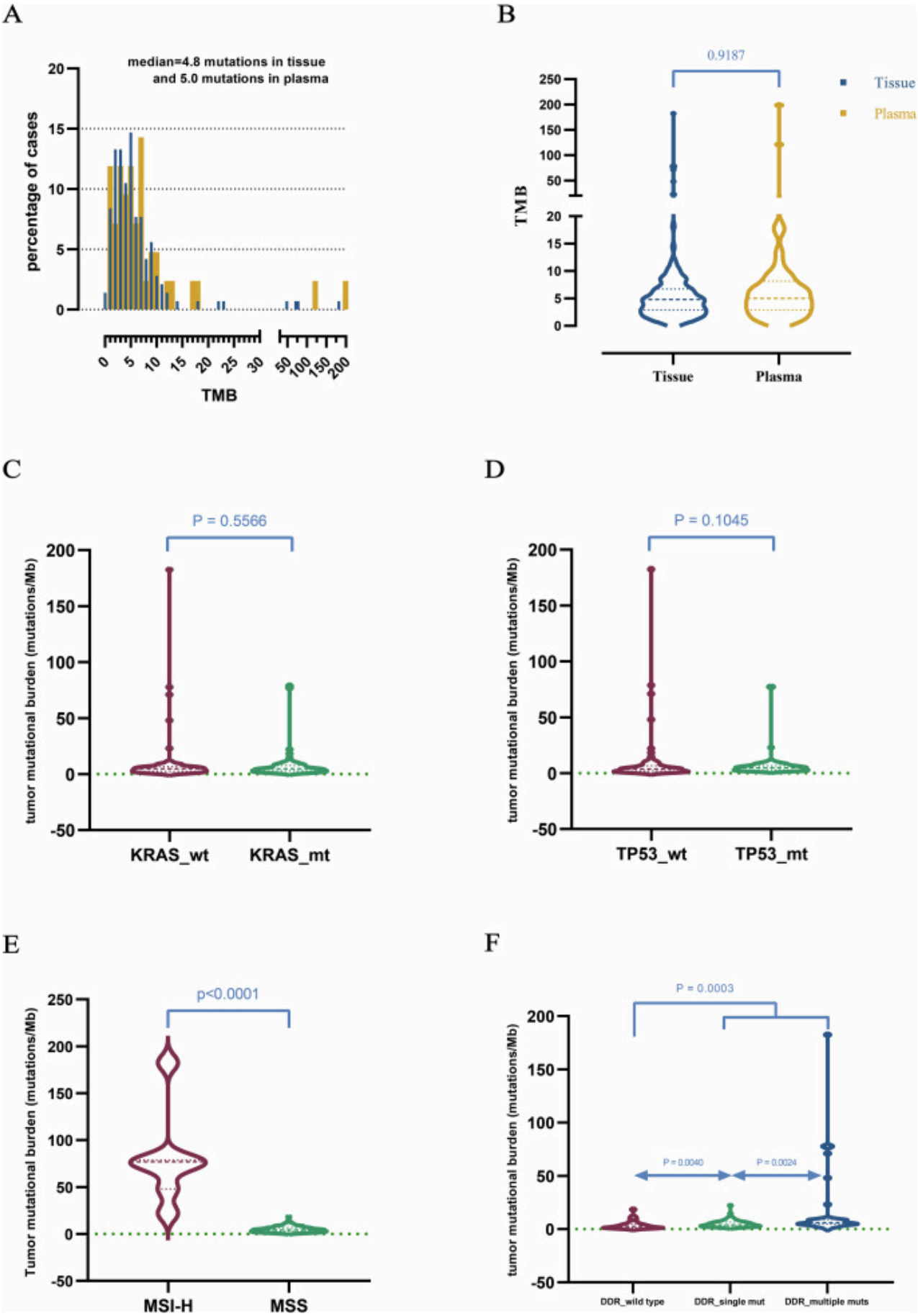

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Fig. 4. Immunogenomic features of SBA. (A)Frequency distribution of TMB in tissue and plasma samples. TMB, tumor mutational burden. (B)Comparison of TMB between tissue and plasma samples. (C-F)Comparison of TMB in KRASmutation, *TP53*mutation, MSI, and DDR pathways statuses. MSI, microsatellite instability. DDR,DNA damage response.

TMB in 143 patients with tissue biopsy was further evaluated. No significant difference between TMB and gender (P=0.4504), age was found (Pearson r=0.0191, P=0.8212), but patients with TNM stage IV had higher tumor mutation burden than those with early stages (P=0.046). However, there was no significant difference in the distribution of TMB between tumors with and without *KRAS* (P=0.5566) or *TP53* (P=0.1045) alterations (Fig. 4C, D. We also analyzed the correlation between TMB and molecular features. Compared with microsatellite stability (MSS) tumors, MSI-H tumors showed strikingly higher TMB (P<0.0001) (Fig. 4E). Morever, patients with DNA damage response (DDR) alterations showed higher TMB than others with DDR wild type (P=0.0003). To exclude the confounding effect of *TP53* alteration, which was a frequent mutation in this cohort, the analysis without *TP53* was repeated, and the result was consistent (P=0.0003). Furthermore, we observed a positive correlation between the number of DDR alterations and TMB (P=0.0040 and P=0.0024 for single alteration versus wild type or multiple alterations, respectively) (Fig. 4F).

Otherwise, the expression of PD-L1 (programmed death ligand 1) by IHC (immunohistochemistry) testing in 55 SBA patients was also assessed (Table S3). Of these, 21 (38.2%) had a tumor proportion score at least 1%, and 4(7.3%) had a score of at least 50%. And 14/43 of duodenal tumors, 3/4 of jejunal tumors, and 4/8 of unknown subtype tumors are PD-L1 positive. We further investigated the association of TPS with other molecular characteristics, such as TMB, frequent alteration, and DDR alteration. None of these showed a significant difference (Fig. S4).

3.6. Agreement of paired tissue and plasma biopsies

The mutation profiles of 6 patients with paired tissue and plasma biopsies at the same timepoint were analyzed. In tissue biopsies, 39 SNVs, 2 CNVs, and 1 SV were detected, while in plasma biopsies, 37 SNVs, 17 CNVs, and 1 SV were detected.

Between tissue and plasma paired samples, most SNVs and SVs were consistently detected, but CNVs were not. Among these, 32 SNVs (72.7%) and 1 SV (100%) were consistent, while only 2 CNVs (11.8%) were. And variant detection in tissue and plasma samples for each patient is as follows (Fig. 5).

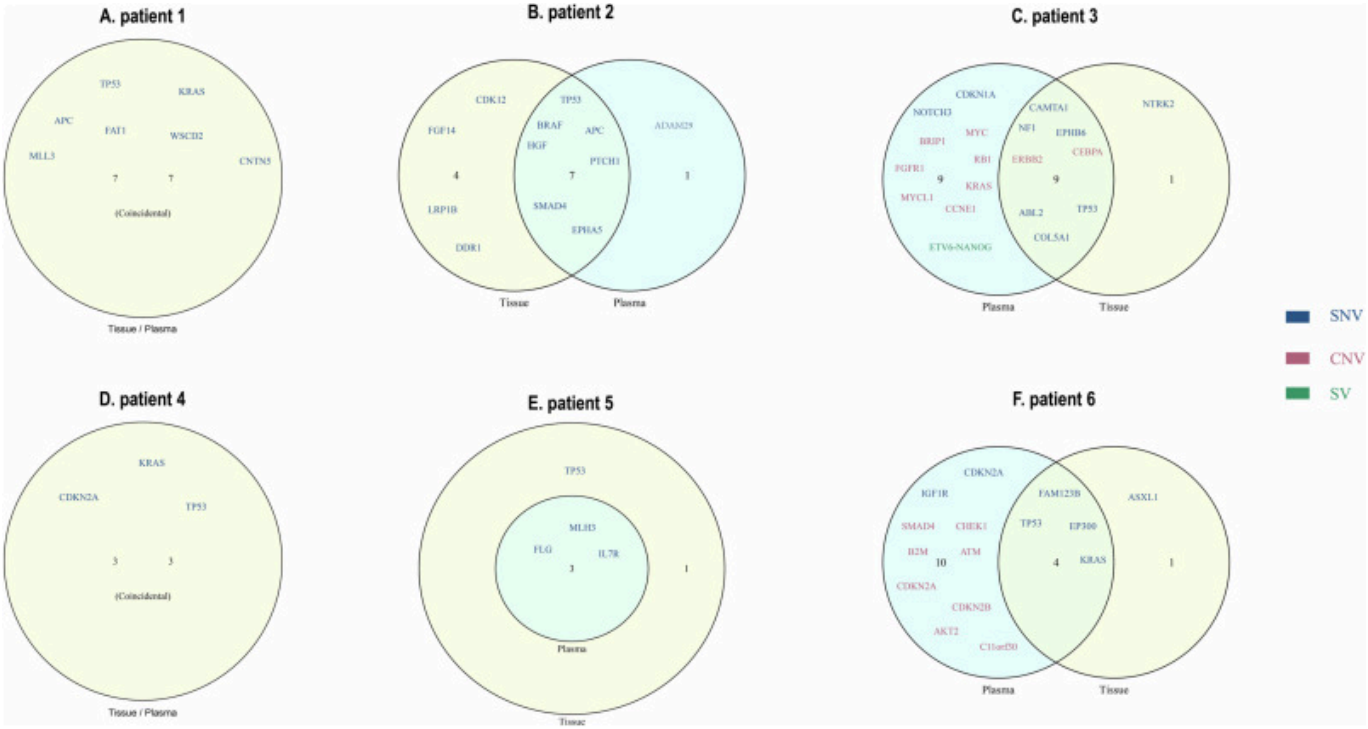

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Fig. 5. Venn diagram of variant detection in tissue and plasma samples: comparison of six patients. The color of the words indicate the type in each alteration. SNV, single nucleotide variant. CNV, copy number variant. SV, structural variant.

Compared to tissue biopsy, plasma biopsy covered 82% SNVs (32/39) and identified 5 additional SNVs, while it covered 100% CNVs (2/2) and identified 15 additional CNVs. Among the actionable alterations found in tissue samples, only one SNV was missed by plasma biopsy. Moreover, plasma biopsy revealed more actionable CNVs than tissue biopsy. The kappa statistic of each mutation was evaluated (Table 2). The kappa values for each gene were high, except for TP53, which had an unconvincing *P* value.

Table 2. Agreement of paired tissue and plasma biopsies.

Mutations	Both positive	Only tissue positive	PPV	Sensitivity	Kappa-value	P-value
	Only plasma positive	Both negative	NPV	Specificity		
	Number of cases(*n*=6)		Percentage(%)			
TP53	5	1	100.0%	83.3%	0.00	1.0000
	0	0	0.0%	#		
KRAS	3	0	100.0%	100.0%	1.00	0.0143
	0	3	100.0%	100.0%		

Mutations	Both positive	Only tissue positive	PPV	Sensitivity	Kappa-value	P-value
	Only plasma positive	Both negative	NPV	Specificity		
	Number of cases(n=6)		Percentage(%)			
APC	2	0	100.0%	100.0%	1.00	0.0285
	0	4	100.0%	100.0%		
EPHA5	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
BRAF	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
NF1	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
FAT1	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
MLL3	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
CNTN5	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
WSCD2	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
EPHB6	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
CAMTA1	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
COL5A1	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
EP300	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
FAM123B	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		

Mutations	Both positive	Only tissue positive	PPV	Sensitivity	Kappa-value	P-value
	Only plasma positive	Both negative	NPV	Specificity		
	Number of cases(n=6)		Percentage(%)			
SMAD4	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
PTCH1	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
HGF	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
IL7R	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
FLG	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		
MLH3	1	0	100.0%	100.0%	1.00	0.1287
	0	5	100.0%	100.0%		

The detection of each mutation for paired tissue and plasma samples. Kappa statistics are used to evaluate the agreement of paired samples.

PPV, positive predictive value. NPV, negative predictive value.

3.7. Comparison of mutations between SBA and left- and right-sided CRC

Mutation data from 148 left-sided CRC (LC) tissues and 147 right-sided CRC (RC) tissues was collected and compared with mutation data from 143 SBA tissues. 3/148 (2.0%) of left-sided CRCs and 25/147 (17.0%) of right-sided CRCs were MSI-H tumors, while 7/125 (5.6%) of SBAs were MSI-H. The mutation spectrum of genes in small bowel adenocarcinoma, left-sided colorectal cancer, and right-sided colorectal cancer were compared. The result showed that SBA was not exactly the same as either of them. The mutation frequencies of 67 genes were significantly different between SBA and left- and right-sided CRC, consisting of 1 gene that differed from LC only, 62 genes that differed from RC only, and 4 genes that differed from both (Fig. 6A). Noteworthy results are as follows (Fig. 6B). The incidence of *KRAS, PIK3CA,* and *MET* mutations in SBA was lower than that in RC patients (FDR=0.0481, 0.0086 and 0.0086), but not significantly different from that in LC patients. On the other hand, *CDKN2A* mutation rate in SBA was higher than that in LC (FDR=0.0291), but not different from RC. The occurrence of mutations in tumor suppressor genes in SBA is markedly lower

than that in LC and RC, for instance *TP53* (FDR=0.0023, 0.0319), *APC* (FDR<0.0001, respectively) and *FBXW7* (FDR<0.0001, FDR=0.0019). However, the mutation rate of the potent tumor suppress *LRP1B* and *POLE* in SBA were similar to that of LC but lower than that of RC (*P*=0.0120, *P*=0.0086). And the frequency of *TCF7L2* mutation in patients with SBA was lower than that in patients with LC and RC (FDR<0.0001, FDR=0.0002), the frequencies of *MLL2* and *FAT2* mutations in SBA were lower than those in RC (FDR=0.0011, 0.0026).

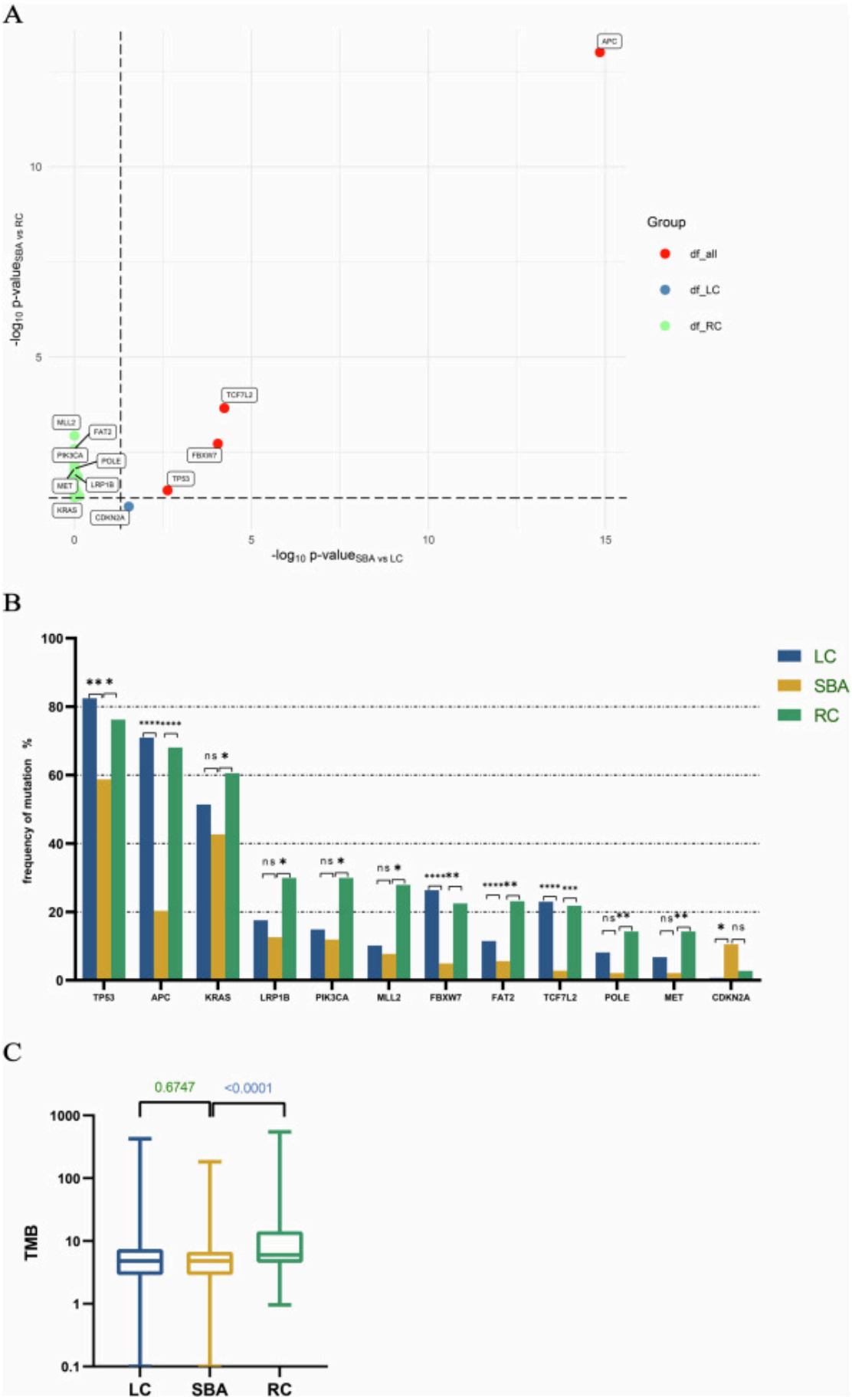

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Fig. 6. Differences in variants between SBA and left- and right-sided CRC. (A) Volcanic maps for different mutation genes between SBA and left- and right-sided CRC. SBA, small bowel adenocarcinoma. LC, left-sided colorectal carcinoma. RC, right-sided colorectal carcinoma. (B) The detection of common gene alterations between SBA and left- and right-sided CRC. (C) Comparison of TMB between SBA and left- and right-sided CRC.

In addition, TMB in 148 LC patients and 147 RC patients with tissue biopsy was further compared with 143 SBA tissue samples. And the result showed that TMB in SBA patients was similar to that in LC (P=0.6747), but lower than that in RC (P<0.0001) (Fig. 6C).

4. Discussion

Our study provides a comprehensive molecular characterization of small bowel adenocarcinoma (SBA) using tissue and plasma biopsies from two cohorts of patients. The most frequently mutated genes and pathways in SBA were compared, as well as the actionable mutations that could inform therapeutic decisions. We also compared the concordance of tissue and plasma biopsies for variant detection and assessed the association of tumor mutational burden (TMB) with clinical and molecular features.

The location of SBA in Chinese patients differed from that in US patients reported by the NCDB. While 60% of US patients had tumors in the duodenum, 80–90% of Chinese patients in our study had duodenal SBA. This suggests that SBA location varies by population. [28]

And our results confirmed that SBA had distinct molecular mechanisms compared with left and right colorectal cancers. The most commonly altered genes in SBA were *TP53*, *KRAS*, *SMAD4*, and *APC*, which are also frequently mutated in colorectal cancer (CRC) and other gastrointestinal malignancies [29,30].However, some differences between SBA and CRC were observed, including the lower frequency of *APC* (20.3% versus 70–80%) mutations with previous reports [13] and the higher frequency of *CDKN2A* mutations, which have not been previously reported (14.0 versus 2–3%). But left-sided colorectal cancer (LC) and right-sided colorectal cancer (RC) should be treated separately according to the differences at the molecular level, clinical manifestations, and treatment methods [31]. Our research further compared the mutation profiles of SBA with specific subtypes of CRC: LC and RC. The results of this study revealed that SBA has a distinct mutation profile from both LC and RC, but is less different from LC than RC. Among these 12 key genes involved in tumorigenesis, 6 in LC were significantly different from SBA, while all in RC were significantly different from SBA. The differences in mutation frequencies of key genes involved in tumorigenesis, such as *KRAS, PIK3CA, MET, CDKN2A, TP53, APC, FBXW7, LRP1B, POLE, TCF7L2, MLL2*, and *FAT2*, indicate that SBA may have different molecular mechanisms and pathways of carcinogenesis from CRC. For example, *KRAS* and *PIK3CA* are oncogenes that activate the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR signaling pathways, respectively. These pathways are important for cell proliferation, survival, and invasion. The lower mutation rates of these genes in SBA compared to RC suggest that SBA may have

less dependency on these pathways for tumor growth and progression. On the other hand, *CDKN2A* is a tumor suppressor gene that encodes p16, a cyclin-dependent kinase inhibitor that regulates the cell cycle. The higher mutation rate of *CDKN2A* in SBA compared to LC implies that SBA may have more dysregulation of the cell cycle and more uncontrolled cell division. And a significant difference in TMB between SBA and RC was observed, but not between SBA and LC.

Several actionable mutations were identified in SBA that could potentially guide treatment selection. For example, we detected *KRAS* mutations in 59.4% (60/143) of tissue samples and 42.8% (18/42) of plasma samples, which could indicate resistance to anti-EGFR therapies [32]. We also found ERBB2 amplification in 2.8% (4/143) of tissue samples and 9.5% (4/42) of plasma samples, which could be a target for anti-HER2 therapies [33]. Moreover, we detected *PIK3CA* mutations in 13.3% (17/143) of tissue samples and 4.7% (2/42) of plasma samples, which could be sensitive to PI3K inhibitors [34]. These results highlight the potential utility of molecular profiling for SBA patients to identify personalized treatment options, and plasma sequencing might be a selective option to adjust treatment for unresectable patients, as no evident difference between tissue and plasma was found.

The association of tumor mutation burden (TMB), a biomarker of immuno-oncology, with clinical and molecular features was examined in SBA. TMB reflects the genomic instability of tumors and may predict the response to immune checkpoint inhibitors. Any significant association between TMB and gender, age, *KRAS,* or *TP53* alterations was not found, but patients with stage IV disease had higher TMB than those with early stages, which may indicate a higher genomic instability and tumor heterogeneity in advanced SBA. TMB was significantly higher in MSI-H tumors than in MSS tumors, which is consistent with previous studies. MSI-H is a molecular marker of defective mismatch repair (MMR) systems, which leads to accumulation of DNA replication errors and increased neoantigens. MSI-H tumors have been shown to respond well to immune checkpoint inhibitors in various cancers, including SBA. We also observed that patients with DDR alterations had higher TMB than those with DDR wild type, and that the number of DDR alterations was positively correlated with TMB. DDR alterations may impair the ability of cells to repair DNA damage and increase the mutation load. DDR alterations have been reported to be associated with a better response to immune checkpoint inhibitors in some cancers, such as ovarian cancer and prostate cancer. However, the role of DDR alterations in SBA immunotherapy remains unclear and needs further validation.

In addition, 21/55 (38.2%) SBA tumors are PD-L1 positive, while about 90% SBA tumors are MSS. Previous studies indicated the ineffectiveness of immune checkpoint inhibitors (ICIs) in MSS SBA [35]. However, immunotherapy can be synergistically combined with other therapeutic modalities to enhance treatment outcomes. Currently, several clinical trials are exploring immune combination therapies specifically for MSS advanced colorectal cancer: TKI and ICIs Combinations (e.g., REGONIVO, REGOTORI, LEAP-005); Radiotherapy and ICIs Combinations (e.g., FRUIT). Further study with immune combinations for SBA needs to be explored.

Finally, concordance and discordance between tissue and plasma biopsies in 6 patients with matched samples were compared, and an outstanding agreement between them was observed. Most SNVs and SVs were consistently detected in both biopsies, but CNVs were additionally detected by plasma biopsy, which was contrary to our expectations and perceptions [36]. This may be due to the bias caused by the small sample size. And in cases where there was only minor discrepancy between tissue and plasma biopsy, we think that it still demonstrated good concordance as long as the critical gene mutations were consistent. It is essential to consider intratumoral heterogeneity. Plasma samples may capture more subclonal mutations that are not detected in tissue samples or may reflect tumor evolution over time. However, two patients' plasma was discovered to contain a considerably higher number of CNVs than comparable tissues. The tumor purity of patient 3's tissue sample was approximately 20%, which is the bare minimum needed for tissue identification. It's possible that the comparatively low tumor purity led to the tissue's CNVs being overlooked. Regarding patient 6, there was liver metastasis to the liver. Given the inter-tumor heterogeneity of the main and metastatic tumors, this may be the cause of the plasma sample's larger number of CNVs than that of the tissue sample.

Plasma biopsy has been widely used as a non-invasive method for liquid biopsy, which can overcome the challenges of tissue biopsy, such as sampling bias, tumor heterogeneity, and invasiveness [37]. Plasma biopsy can also provide real-time information on tumor dynamics and treatment response. Therefore, plasma biopsies may not be able to replace tissue biopsies completely, but they could complement them by providing a non-invasive and dynamic assessment of tumor status. And plasma biopsies may be useful for monitoring disease progression and response to therapy.

However, our study also has some limitations: (i) Insufficient data for jejunal and ileal tumors. The majority of tumors in our dataset are duodenal tumors (90%), leaving only a small subset (10%) as jejunal and ileal tumors. Subgroup analyses based on tumor location are limited; (ii) Limited paired samples. Small bowel cancer is indeed a rare malignancy, and our stringent sample selection process further limits the availability of paired samples. (iii) Lack of patient follow-up information. As a retrospective study, subsequent treatment data is not available beyond the initial detection of actionable mutations. Therefore, further studies with larger cohorts, prospective designs and clinical outcome data are needed to validate our results and translate them into clinical practice.

In conclusion, this study provides a comprehensive molecular characterization of SBA using tissue and plasma biopsies. We identified the mutation spectrum, actionable alterations, signaling pathways, and immunological features of SBA, and revealed that SBA has a distinct mutation spectrum from left-sided and right-sided CRC. Furthermore, we demonstrated that plasma biopsy is a feasible and reliable method for detecting SNVs and SVs in SBA, but has limited sensitivity for detecting CNVs. Our findings may have important implications for the diagnosis, prognosis, and treatment of SBA patients.

CRediT authorship contribution statement

Dan Yu: Validation, Resources, Project administration, Investigation, Data curation, Conceptualization. **Jianzheng Wang:** Validation, Project administration, Investigation, Conceptualization. **Bo Zheng:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Mingming Yuan:** Writing – review & editing, Software, Project administration, Conceptualization. **Dejian Gu:** Software, Project administration, Investigation, Conceptualization. **Rongrong Chen:** Validation, Resources, Project administration, Conceptualization. **Xiao-Bing Chen:** Validation, Supervision, Resources, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

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Data availability

The data that support the findings of this study are available on request from the corresponding author.

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