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Gaining insights into relevance across cancers based on mutation features of TP53 gene

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ABSTRACT

The tumor suppressor gene TP53, one of the most frequently mutated genes, is recognized as the guardian of genome and can provide a significant barrier to neoplastic transformation and tumor progression. Traditional theory believes that TP53 mutations are equal among cancer types. However, to date, no study has explored the TP53 mutation profile from a holistic and systematic standpoint to discovery its relevance and feature with cancers. Mutation signature, an unbiased approach to identify the mutational processes, can be a potent indicator for exploring mutation-driven tumor occurrence and progression. In this research, several features such as hotspots, mutability and mutation signature of somatic TP53 mutations derived from 18 types of cancer tissues from cBioPortal were analyzed and manifested the organizational preference among cancers. Mutation signatures found in almost all cancer types were Signature 6 related to mismatch repair deficiency, and Signature 1 that reflects the natural decomposition of 5-methylcytosine into thymine associated with aging. Meanwhile, several signatures of TP53 mutations displayed tissue-selective. Mutations enriched in bladder, skin, lung cancer were associated with signatures of APOBEC activity (Signature 2 and 13), alkylating agents (Signature 11), and tobacco smoke (Signature 4), respectively. Moreover, Signature 4 and 29 associated with tobacco smoking or chewing found in lung, sarcoma, esophageal, and head and neck cancer may be related to their smoking history. In addition, several digestive cancers, including colorectal, stomach, pancreatic and esophageal cancers, showed the high correlation in context and mutation signature profiles. Our study suggests that the tissue-selective activity of mutational processes would reflect the tissue-specific enrichment of TP53 mutations and provides a new perspective to understand the relevance of diverse diseases based on the spectrum of TP53 mutations.

1. Introduction

TP53, a master tumor suppressor gene with the mostly frequent mutations and a driver gene affecting the accumulation of mutations, is recognized as the guardian of the genome, and plays a critical role in cancer biology by participating in basic events among cancer initiation and progression [1,2]. The prevalence of TP53 mutation occurred in almost all human cancers including breast, liver, prostate, bladder, colorectal, stomach, esophageal, lung, ovarian, brain, pancreatic cancers and so on [2]. Although the relevance of TP53 dysfunction, interaction network and oncogenesis has been widely explored, a systematic analysis of TP53 mutations is lacking. In clinical studies, all TP53 mutations are obedient to traditional equivalent theory, which considered no difference among various cancer types [3]. However, an increasing understanding and evidence supports an antithetical hypothesis, indicating that distinct mutations on TP53 affect different activities and properties [4,5]. Whether all mutations or mutation patterns are also unequal among multifarious cancers is ambiguous. It is worthy to furtherly understand and explore the mutation patterns of TP53 and its correlation with diverse cancers.

The main mode of TP53 inactivation is non-synonymous single nucleotide substitutions, followed by small insertions, deletions and fewer rearrangements, which may be caused by various forms of DNA replication and repair mechanisms infidelity [5], endogenous, and exogenous mutagens [6]. Because DNA damage and repair processes do not uniformly affect the genome, some mutations are more frequent than others. Meanwhile, the frequency of TP53 mutations and whole-genome mutational burden accompany with TP53 mutation are

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also highly variable depending on the type of cancer [6,7], suggesting that tissue type is an important factor contributing to tumor heterogeneity.

Mutation signatures have been general accepted and applied as a reliable and quantifiable approach to measure the proportion of distinct mutational mechanisms in cancers [8], based on the six patterns of signal base substitution (C:G > A:T, C:G > G:C, C:G > T:A, T:A > A:T, T:A > C:G and T:A > G:C) [9]. Previously, some studies have depicted the spectrum mutations in individual or several relevant cancers, revealing a significant heterogeneity of the TP53 spectrum across different cancer types [10]. The TP53 spectrum of skin carcinomas displays the enrichment of mutations in C:G > T:A and CC:GG > TT:AA [11]. In liver cancers, it is demonstrated that C:G > A:T transversions are common, and these mutations are believed to be associated with aflatoxin [12]. However, these researches just focus on single cancer or several cancers with similar phenotype, other than considered as a systematic, holistic, connected unity.

In this study, we have capitalized on the integrated somatic databases including 18 cancer types from cBioPortal (http://www.cbioportal.org) and utilized the frequency, type and context of mutations in the TP53 coding region to extract mutation signature and mutability. It is conducive to reflecting the driving mutational processes and exploring the new perspective, in order to understand the relevance of diverse cancers based on the spectrum of TP53 mutations and provide the new insight for clinic diagnosis and treatment.

2. Materials and methods

2.1. Bioinformatic analysis

2.1.1. Mutation dataset collection and filtration

The dataset of somatic TP53 mutations in exons from 165 projects were collected from cBioPortal (http://www.cbioportal.org), which was associated with 18 cancer tissues. The clinical information including smoke status, survival probability and survival time of samples with or without TP53 mutation was also obtained from cBioPortal respectively. The number of mutations were counted and cancer types were ranked in decreasing order of mutation frequency. The types of mutations were classified as missense, non-sense, frameshift, splice, in-frame shift, and fusion, and calculated their occupation. Single substitution missense mutations located in TP53 exons were selected as processing object after removing the repeated data among projects. The reshape2 and ggplot2 packages of R software were used to display the frequency distribution of TP53 mutation hotspots; while reshape2, ggplot2 and scatterpie packages were applied to show the protein change hotspots and their types of changes.

2.1.2. Survival analysis

The survival rate analyses were performed and extracted by R software with the survival package to figure out the changes brought from TP53 mutations among cancers. The survival curve was drawn and visualized through survminer package. $P < 0.01$ was considered as statistical significance.

2.1.3. Mutability analysis

The context-dependent mutational probability among cancers was calculated and extracted by MutaGene (https://www.ncbi.nlm.nih.gov/research/mutagene/package). Cluster analysis was based on Pearson correlation.

2.1.4. Mutation signature analysis

The mutation signatures among cancers were classified and the proportion of each mutation signature was calculated by deconsrtuctSigs package [13]. The input data was a data frame consisting of mutational data of the tumor sample set, including the genomic position, base change of each mutation, and the sample identifier.

```
sigs.input < - mut.to.sigs.input(mut.ref = sample.mut.ref, sample.id = "Sample", chr = "chr", pos = "pos", ref = "ref", alt = "alt")

output.sigs = whichSignatures(tumor.ref = sigs.input, signatures.ref = signatures.nature2013, sample.id = "cancer_name")
```

Cluster analysis was based on Pearson correlation.

2.2. Statistical methods

Graphpad Prism 8 and ggplot2 were applied for data analysis and graphic visualization.

3. Results

3.1. The somatic TP53 mutations vary across cancer types

165 projects including 18 tissues were selected, in which 19,175 cases carry somatic TP53 mutations in coding region (Fig. 1A). In generally, somatic TP53 mutations were common in various tissues and cancers with rates from 5%–85%. Somatic TP53 mutation carriers accounted for over 50% in ovarian, esophageal, colorectal, head and neck, lung, ampullary, stomach and gallbladder cancers, and between 20 and 50% in pancreatic, bladder, breast, sarcoma, brain, liver, skin, prostate cancers (Fig. 1B). TP53 had the highest mutation rate in ovarian and esophageal cancer and the lowest rate in kidney and leukemia. Moreover, a significantly inferior overall survival rate displayed in patients with TP53 mutations in comparison to those without TP53 mutations in several cancer tissues, such as breast, pancreas, prostate, head and neck, kidney, and lung (Figs. 1C and S1).

3.2. The hotspots of somatic TP53 mutations differ among human cancers

The functional impact and spatial distribution of somatic TP53 mutations were analyzed. The majority of TP53 mutations were missense mutations occupying 64.33%, followed by 13.68% non-sense, 12.49% frameshift (9.34% deletion and 3.15% insertion), 7.06% splice, 2.08% in-frame shift (1.69% deletion and 0.40% insertion) and 0.37% fusion (Fig. 2A). Getting rid of repetitive data, 9481 cases with single missense mutation were selected for downstream analyses. Based on the spatial distribution analysis, 96.48% missense mutations were located in the DNA-binding domain (DBD) (Fig. 2B), which occupied 48.60% in the length of TP53. Even though two transactivation domains, TAD1 and TAD2, occupied 23% in the length of TP53, only 1.09% of TP53 missense mutations occurred in this region. The mutation rate in the oligomerization domain (OD) was approximately 1.93%, which occupied 8.16% in the length of TP53 (Fig. 2B). Based on the hotspot analysis of mutation sites, several universal hotspots were found among cancers, including c.818C > T, c.743C > T, and c.524C > T (Fig. 2C), leading to the well-acknowledged protein change R273H, R248Q, and R175H respectively (Fig. S2). Meanwhile, several hotspots displayed the preference of tissue, such as c.813C > T in bladder cancer, c745C > A in liver cancer and c.722A > G in skin cancer (Fig. 2C). Our results elaborated parsimoniously a distinct phenomenon for the enrichment of TP53 missense mutations generally and tissue-specific hotspot mutations among cancers.

3.3. Context-dependent mutational probability displays the tissue-specific among cancers

The frequency of trinucleotides in TP53 coding region was counted, and an inhomogeneous distribution was found with the highest enrichment in CCA, CCC and CTG (Fig. 3A). However, the inconsistent result, derived from the frequency of trinucleotides based on TP53 missense mutations, suggested that the mutated sites displayed the preference of trinucleotides accompanied with tissue-specific (Fig. 3B).

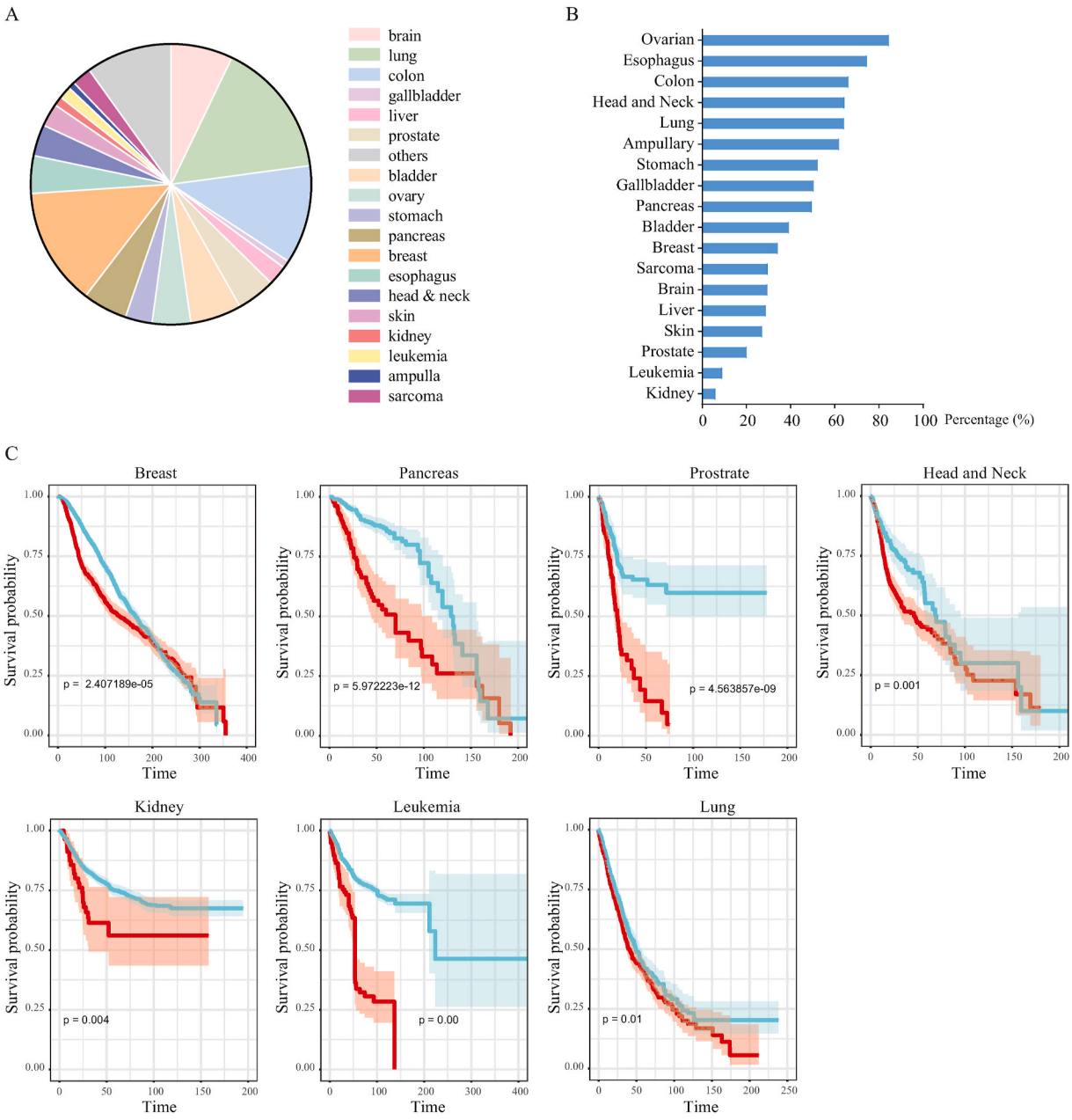

Fig. 1. TP53 mutations prevalence among cancers. (A) Pie chart showing the composition of samples with somatic TP53 mutations in each cancer sub-type. (B) The tumor spectrum with somatic TP53 mutations among 16 cancer types based on the mutational rate. (C) The comparation of survival rate with or without TP53 somatic mutation among cancers. The red line corresponds to the survival with TP53 mutation, and the blue line corresponds to the survival without TP53 mutation. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Meanwhile, the result of clustering showed the highest correlation among colorectal, pancreatic, prostate, brain and stomach cancers (Fig. 3C), which displayed the similar preference of mutation context in NCG. Lung, esophageal, ovarian and head and neck cancers showed the tight relationship with the mutated trinucleotides enrichment in NCN, while bladder and breast cancers displayed the preference in NCG and TCN. Moreover, skin cancer performed an extrusive predilection in TCN.

3.4. Mutation signature reveals the tissue-selective among cancers

6 patterns of mutation types were analyzed and the overall proportions were highly consistent in almost all cancers. The C: G > T: A mutations were predominant except that the liver and lung were rich in C: G > A: T mutation (Fig. 4A).

The projections of mutational signatures displayed that Signatures 1 and 6 occurred in almost all cancer types, while Signatures 2, 3, 4, 11, 13, and 18 performed tissue-selective. Signature 2 and 13 only occurred in bladder cancer, while signature 3, 4, 11 and 18 were only discovered in gallbladder cancer, lung cancer, skin cancer, and kidney cancer, respectively (Fig. 4B). Moreover, signature 5, 7, 15, 16, 21, 24, 26, and 29 were discovered in multiple cancers. Based on the complexity and composition analysis of signatures among cancers, in most cancers at least two kinds of mutational signatures were observed (Fig. 4B). Colorectal and stomach cancers shared the same minimal pattern, only consisting of signature 1 and 6 (Fig. 4B). The signature pattern of ovarian cancer was similar with prostate cancer, containing signature 1, 6, and 16. Liver, lung and skin cancers showed more complex constitution, containing over 5 types of signatures (Fig. 4B). More signature patterns contained suggested the more mutation processes participated.

Then through clustering the signature patterns among cancers, 11

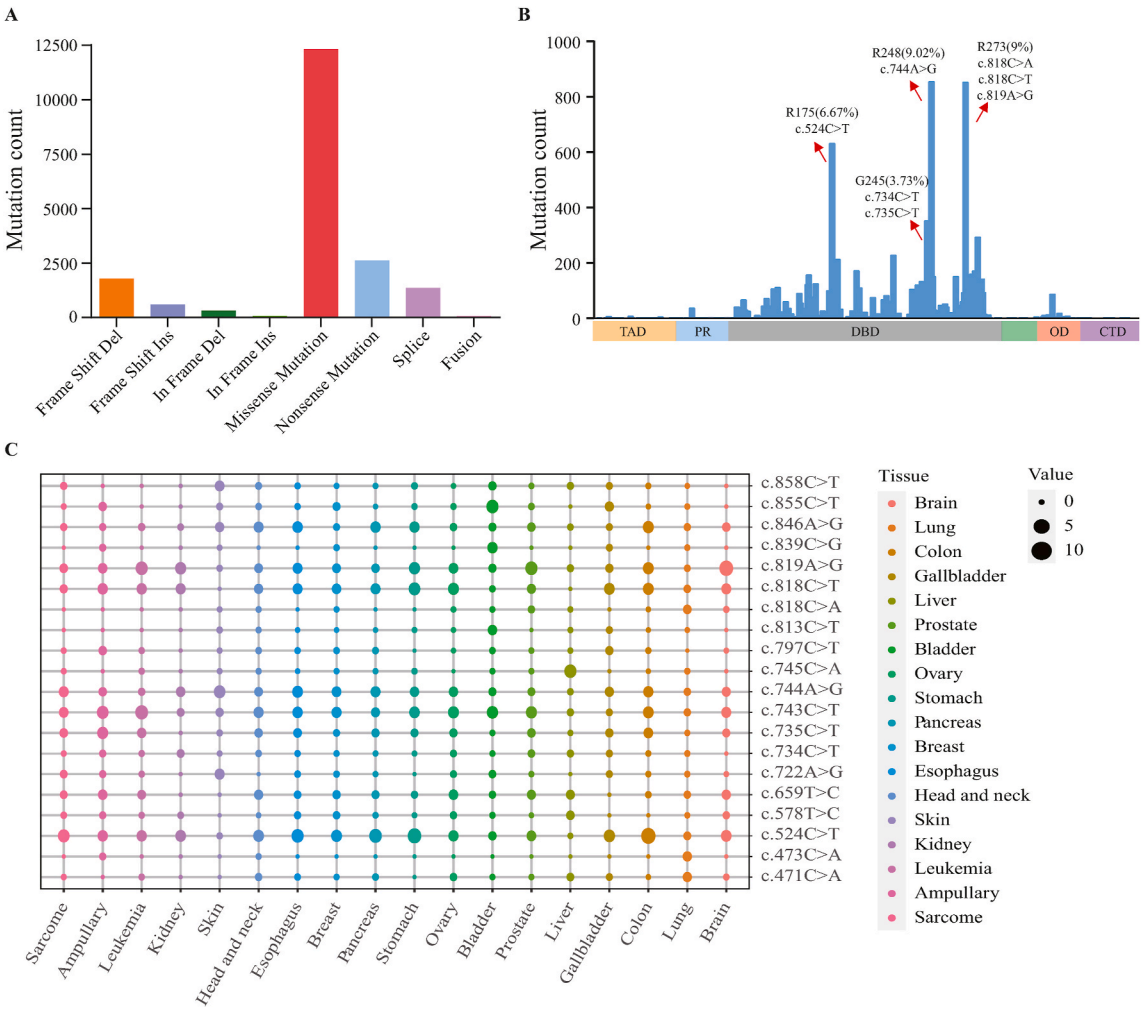

Fig. 2. Functional impact of somatic TP53 mutations in human cancers. (A) Histogram showing the proportion of the different effect due to TP53 somatic single-nucleotide substitutions in encoding region. (B) Histogram displaying the position of somatic triplet codon point mutations located in the coding region of TP53. (C) Histogram displaying the hotspots of TP53 mutation among cancers. The circle size represents expected mutability calculated by MutaGene.

types of cancers, including colorectal, stomach, prostate, brain, leukemia, pancreatic, esophageal, head and neck, ovarian, breast and sarcoma cancers showed the tight connection. It is noteworthy that several digestive cancers displayed the highest correlation, including colorectal, stomach, pancreatic and esophageal cancers (Fig. 4C).

It's interesting that signature 4 and 29, associated with tobacco smoking or chewing, were found in lung, esophageal, sarcoma and head and neck cancers (Fig. 4B, Fig. S3). The smoking history confirmed that the frequency of TP53 mutations in smokers was higher than those never smoking in these cancers (Fig. 4D). The mutation frequency of people who still smoking was higher than that of people who ever smoked in lung and esophageal cancer (Fig. 4D). The mutation frequency of people smoking heavily was higher than those smoking lightly in lung cancer (Fig. 4D).

4. Discussion

TP53 plays a role of central junction that receive, integrate, and transmit multiple signals, generated during various stress events, to keep cell and tissue homeodynamics [14]. Our findings provide a comprehensive catalogue of somatic TP53 mutation across human cancers, and analyze the connection and specificity among cancer types underlying the frequency, survival rate, mutation context, mutability and mutation signature. Our results break the traditional equality theory and find that TP53 mutation and mutation pattern have organizational preference. It is helpful to explain the potential mechanism of cancer occurrence and development, and explore the connection among cancers.

At present, 30 distinct mutational signatures are identified that describe the possibility of obtaining a specific base change and the activity of an underlying mutational process, taking consideration of the trinucleotide mutation context. Of the 30 mutational signatures that have been uncovered, 17 have been attributed specific etiologies. Previously, mutation signature has been often applied to mutations in the entire genome, and rarely focuses on a certain gene alone. In our study, it is proved that the projection of mutation signature based on TP53 mutations can also efficiently perceive the potential mechanism participating in introduction of TP53 mutations during the formation and development of cancers [15,16]. Whether the mutation signatures based on TP53 mutations can reflect and represent the overall cancer to a certain extent, so as to server as a potent and effective cancer classification index is worthy to be considered.

Signature 6, associated with DNA mismatch repair (MMR) defect, represents the universal mechanism of DNA damage and DNA replication interacting with most processes to introduce mutations. That it widely occurs among cancers indicates that all cancer types share the same process represented by Signature 6 to introduce TP53 mutations, which is consistent with the mutation trend in overall mutations provided from COSMIC. Signature 1 is associated with age and spontaneous deamination of 5-methylcyotosine, revealing that age is also a dominant factor for the accumulation of mutation in most cancers. The relatively

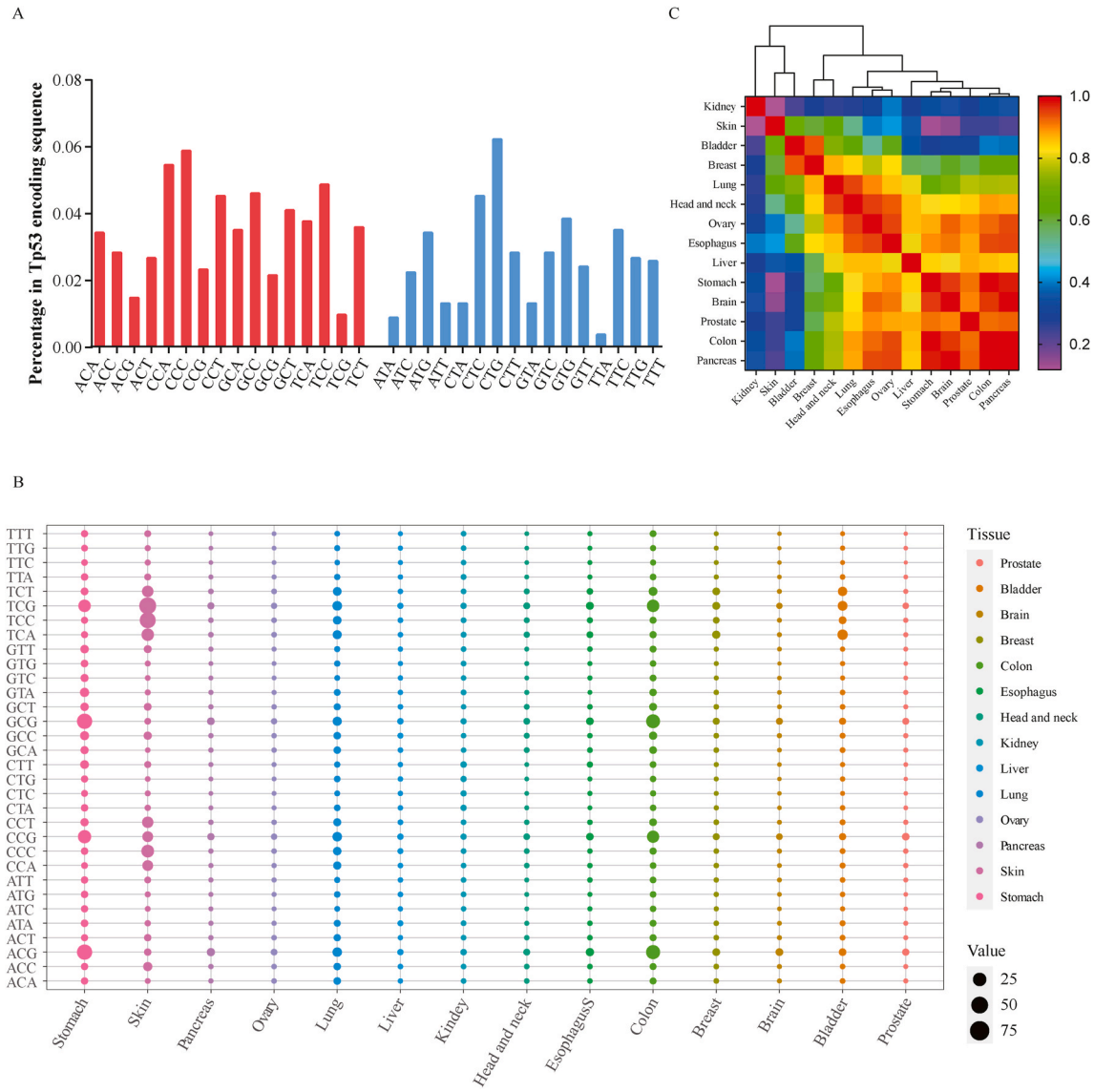

Fig. 3. Mutability of TP53 mutation among cancer tissues. (A) The original frequency of TP53 trinucleotide contexts in encoding region. (B) The expected mutability of 32 mutation patterns among cancers. The circle size represents expected mutability calculated by MutaGene. (C) The Hierarchical clustering analysis indicating the correlation among cancers through Pearson correlation co-efficient analysis.

elevated rate of spontaneous deamination of 5-methyl-cytosine can result in C > T transitions and predominantly occur at NCG trinucleotides [8], which can explain the enrichment of TP53 mutations in C > T and NCG trinucleotides in almost all cancers in our findings.

Signature 2, 3, 4, 11, 13 and 18 displayed tissue-specific, in which cancers with signature2, 4, 11, 13 is consistent with COSMIC consensus. That Signature 2 and 13 both present in bladder cancer is both attributing to activity of AID/APOBEC family. It has been reported that Signature 2 discovered in the overall mutational load of 412 muscle-invasive bladder cancers was associated with APOBEC-signature mutagenesis [17]. Signature 13 is most common in bladder cancers according to COSMIC, which is conformed to the specificity in bladder discovered in our result. It has been proposed that activation of AID/APOBEC cytidine deaminases is due to viral infection, retrotransposon jumping or to tissue inflammation. Mutations with similar patterns to Signatures 2 and 13 are commonly seen in local hypermutations in certain cancers (called kataegis), which may also be related to the AID/APOBEC enzyme. Signature 11, associated with alkylating agents induced mutation pattern or associated with the alkylating agent temozolomide treatment, has been identified in melanoma and glioblastoma cancer based on COSMIC, which is also consistent with our discovery in skin cancer. Signature 4 and 29 are both proved to be related to tobacco smoking or chewing. The signature 4 is observed in lung adeno, squamous and small cell carcinomas, head and neck squamous, and liver cancers in COSMIC [8]. In our results, Signature 4 occurs in lung cancer and Signature 29 occurs in esophageal, sarcoma and head and neck cancers, which is greatly consistent with the smoking history. Meanwhile, Signature 24, associated with aflatoxin, is contributed to C: G > A: T reported in COSMIC, which greatly interprets the higher observation of C: G > A: T mutation pattern in liver and lung cancers in TP53 mutations. However, signature 3 and 18 are different between our results and COSMIC, which may be attributable to differences in the power to extract signatures. The consistent mutational signature distribution between TP53 and overall tumor indicates the similar mutational mechanism to introduce mutations, which suggests that mutation signature based on TP53 mutations can represent the overall mutation features to some extent.

The preference of the features including hotspot sites, mutated context and mutation signature that manifests as enrichment of tissue-specific TP53 mutations and the tissue-selective activity of mutational

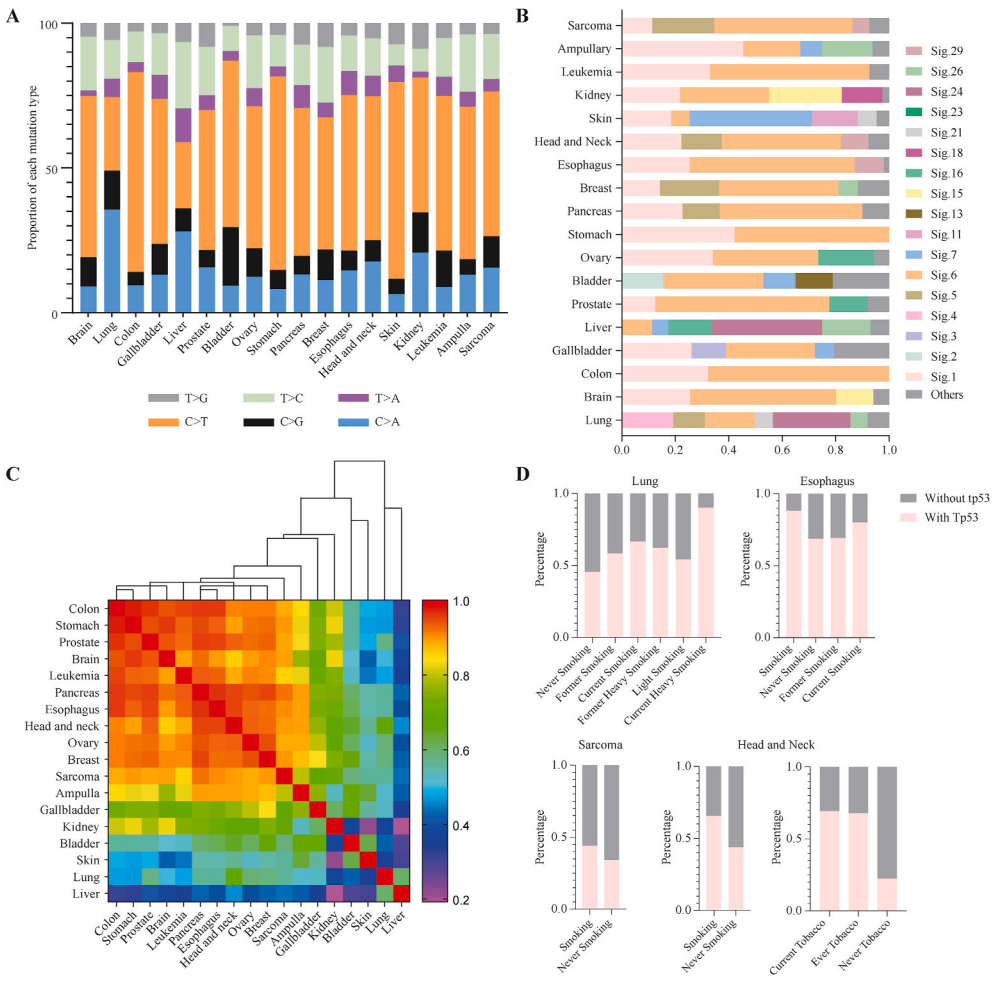

Fig. 4. Mutation signatures of TP53 among cancer tissues. (A) The constitution of 6 mutation patterns among cancer types. (B) The proportion of mutation signatures among cancers. Mutation signatures were attained from the COSMIC mutation signature consensus database (http://cancer.sanger.ac.uk/COSMIC/signatures). (C) The Hierarchical clustering analysis indicating the correlation among cancers through Pearson correlation co-efficient analysis. (D) The smoking history of cancers with Signature 4 and 29.

processes among cancers, suggesting that mutation signatures based on TP53 mutations can be a credible, potential index to classify cancer types. The type of changes in the triplets for each amino acid and the resulting changes in its amino acid both suggest that there are shared or unique selection preferences among different tumors, which may be due to self-adaptation and natural accumulation during the progression of various cancers. Some hotspots are also observed in research based on the COSMIC Whole Genome Dataset [18], among which the hotspots of c.524C > T, c.659C > T, c.743C > T, c.818C > T leading to R175H, Y220C, R248Q, and R273H protein changes have also been disclosed. Our results have found that these sites have a higher mutation frequency among various cancers, which suggests that these sites may be shared preference sites among tumors. We have observed that TP53 mutations are mainly missense mutations. To explain whether this phenomenon is the characteristic of TP53 or the sharing mode of other tumour suppressors and in proto-oncogenes, we also further have counted the other three genes in the p53 signaling pathway, CDKN2A, MDM2, and MDM4. Although MDM2 and MDM4 show consistency, the main mutation type of CDKN2A is truncation, other than missense mutation. Therefore, we believe that the mutation types of different cancer-related genes are not limited to one pattern, but the main choice depends on the function of these genes in inhibiting or promoting cancer process and the resistance to mutations that destroy this function. We observed that missense mutations of TP53 are mainly enriched in the DNA binding domain, which may be due to the fact that we only focused on mutations with functional effects. The rest p53 domains are intrinsically disordered regions (IDR), so a single amino acid change will not have a profound effect on the function of p53, therefore has not been paid attention to in different types of cancer. The clustering analysis of mutation signature and mutability provide the correlation among cancer types. Colorectal and stomach cancer shows the highest relevance in both statistical methods, and prostate, pancreatic, esophageal and brain cancers are close to them, in which colorectal, stomach, pancreatic and esophageal cancers are digestive cancers. The complex heterogeneity of mutation signatures suggesting that more repertoire of mutational processes participate in the introduction of TP53 mutations in lung, liver, and skin cancers, which contain more than 5 kinds of mutation signatures. Both the complexity and composition analysis of signatures revealed the relevance among cancers to some extent, in which the similarity can explain the common process among cancers, and the specificity may be applied to find out the unique potential mechanism of occurrence and development for a certain cancer or a certain type of cancer.

Rough classification of cancer types restricts our opportunities for exploring correlation between cancer subtypes and somatic TP53 mutations. It's reported that the frequency of TP53 mutation is different in subtypes of lung cancer, occupying 50% in large cell carcinoma (LC) and adenocarcinoma (Adc), and 80% in small cell lung cancer (SCLC) and squamous cell carcinoma (SCC) [19]. Meanwhile, it's confirmed that p53 mutates in the late stage of tumorigenesis process or plays a noteworthy role in advanced stages, leading to a more aggressive and invasive tumor in certain cancers [20]. In future studies, in order to more accurately and comprehensively recognize the relationship between TP53 mutations and various cancers, more complete cancer types and stages, larger cohorts of samples with detailed clinical information including prognosis, age of onset, etc [21], histological data, functional analysis and survival analysis should been taken into consideration.

5. Conclusions

Our findings are established in a holistic and systematic standpoint based on TP53 mutations to explore the connection and specificity among cancers. we have confirmed that TP53 mutation and mutation pattern are unequal among cancers. The composition of mutation signature suggests a complex repertoire of mutational processes in cancers. The relevance among cancer types based on mutation signatures of TP53 mutations can help to illuminate the common and unique mechanisms during the formation and development of cancers. Furtherly, because that the subtype and stage of tumor are also important factors affecting the frequency of TP53 mutations, the chronology of TP53 mutation should be also considered to explore and assess the relevance among various type and subtype cancers by longitudinal analyses. In the future, precision medicine clinical studies focused on patient selection will be needed to evaluate whether the existence of signature composition can better select patient for medical treatment, and whether targeted therapy based on the signature mechanism can also provide patients with the suitable approaches and benefits.

Data availability

The bioinformatic data used to support the findings of this study is derived from cBioPortal (http://www.cbioportal.org).

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.bbrep.2021.101165.

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