Cell. Mol. Biol. (ISSN: 1165-158X)

Journal Homepage: www.cellmolbiol.org

Cellular and Molecular Biology

Original Article

Characterization of the prognostic, diagnostic, and immunological roles of DSCC1 and its genomic alteration and instability in human cancers

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Article Info

Article history:

Received: November 15, 2023
Accepted: February 27, 2024
Published: April 30, 2024

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Abstract

DNA replication and sister chromatid cohesion 1 (DSCC1) exerts various functions including sister chromatid cohesion. DSCC1 overexpression plays an important role in cancer development, such as in colorectal, breast, and hepatocellular cancers. The specific role of DSCC1 in tumor progression remains largely unknown, necessitating a pan-cancer investigation to understand the potential function of DSCC1 in various cancers. In this study, we obtained data on physiological conditions, transcriptional expression, survival prognosis, genomic alteration, genomic instability, enriched pathways, immune infiltration, and immunotherapy from The Cancer Genome Atlas, The Genotype-Tissue Expression, cBioPortal, and other publicly available databases to systematically characterize the oncogenic and immunological roles of DSCC1 in 33 different cancers. We found that DSCC1 expression was upregulated at both mRNA and protein levels in various cancers. Additionally, DSCC1 expression was associated with higher tumor stage and grade in specific cancers. DSCC1 was a potential pan-cancer prognostic biomarker for its close association with patient prognosis and a diagnostic biomarker for its high predictive value in distinguishing tumor tissues from normal tissues. DSCC1 was universally amplified across different cancers and tightly associated with genomic instability. Moreover, DSCC1 had a close relationship with tumor immune cell infiltration; thus, it could be used as a potential biomarker for predicting the response and survival of patients with cancer who receive immune checkpoint blockade treatment. To sum up, our study revealed that DSCC1 is a promising target for tumor therapy.

Keywords: DSCC1, Genomic alteration, Genomic instability, Pan-cancer, Prognosis, Tumor immunity.

1. Introduction

Cancer is the leading cause of mortality worldwide and a major cause of decreasing human life expectancy [1]. As a complex group of genomic diseases, cancers primarily involve molecular malformations including somatic mutations, copy number alterations, changes in transcriptional expression, and epigenetic variations [2]. In this regard, The Cancer Genome Atlas (TCGA) platform was built to characterize the molecular events occurring in cancers; this database collects genome sequencing data from more than 11,000 samples for 33 different cancers, and these data greatly facilitate the users to comprehensively investigate molecular aberrations involved in human cancers by applying genomic technologies [3]. A genetic pan-cancer analysis provides a macroscopic, multi-faceted understanding of the mechanisms underlying genomic alterations in cancers.

DNA replication and sister chromatid cohesion 1 (DSCC1), also known as DCC1 (defect in chromosome cohesion 1), is an essential component of the Ctf18-DSCC1-Ctf8-replication factor C (Ctf18-RFC) complex and plays an important role in loading the proliferating cell nuclear antigen (PCNA) clamp onto DNA replication forks in an ATP-dependent manner [4]. During the formation of this complex, the last winged-helix DNA-binding domain of DSCC1 present in its C-terminus binds to polymerase ε [5]. DSCC1 is an important component for maintaining intact genome stability [6]. Despite these vital functions of DSCC1, it may also play a unique role in cancer development. DSCC1 overexpression and its role in promoting tumor cell proliferation have been reported in colorectal cancer [7], hepatocellular carcinoma (HCC) [8], and breast cancer [9]. However, the specific roles of DSCC1 in cancer development have been poorly explored. Moreover, available evidence for the oncogenic role of DSCC1 is restricted to a few cancer types. Therefore, a thorough pan-cancer investigation is necessary to understand the potential function of DSCC1 in different cancers from diverse aspects.

In the current research, we comprehensively analyzed

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Doi: http://dx.doi.org/10.14715/cmb/2024.70.4.32

literature data on the expression, prognosis, genomic alteration, genomic instability, and immune infiltration of DSCC1 through a pan-cancer analysis. Additionally, we explored the potential biological functions (oncogenic and immunologic functions) of DSCC1 through a bioinformatics approach in various cancers. The findings of this study are expected to highlight the clinical significance of DSCC1 in cancer therapy and to guide subsequent DSCC1 research in the field of oncology.

2. Materials and methods

2.1. Analysis of DSCC1 physiological conditions

The Protter database (http://wlab.ethz.ch/protter/start/) was used to characterize the topology structure of DSCC1, followed by the explorations of DSCC1-relevant subcellular location and single-cell variation analyses operated on the human protein atlas (HPA) database (https://www.proteinatlas.org/). The Genotype-Tissue Expression (GTEx) (https://www.gtexportal.org/) project provided an overall view of DSCC1 expression in normal human tissues. Additionally, the String database, an online platform, was used to predict the functional associations between DSCC1 and other interactive proteins, and the minimum interaction score was set as 0.900. Finally, the Open Targets platform facilitated the identification of DSCC1-associated diseases by integrating publicly available datasets, with 0.05 being the minimum score.

2.2. DSCC1 expression and prognostic analysis in pan-cancer

We obtained gene expression profiles of pan-cancer tissues and normal tissues in a total of 15,776 samples from the UCSC XENA (https://xena.ucsc.edu/, derived from the TCGA database). The normalized RNA sequencing data in the transcripts per million (TPM) format was processed through the Toil algorithm. Then the TPM format was log2 converted for expression analysis (log_2TPM+1). Through the "Clinical" module of the TISIDB website (http://cis.hku.hk/TISIDB/index.php), we attempted to associate the DSCC1 expression trend with increasing tumor grades and stages. Additionally, we used the HPA database to obtain immunohistochemical images of the DSCC1 protein in both tumor and normal tissues. Data obtained from the UALCAN database (https://ualcan.path.uab.edu/index.html) was quantitatively compared for DSCC1 proteomics expression.

We downloaded prognostic information on all patients with cancer from the TCGA database. The correlation between DSCC1 expression and survival outcomes, including overall survival (OS), disease-specific survival (DSS), and progression-free interval (PFI) in each patient, was estimated through univariate Cox regression analysis and log-rank test. With the R package "forestplot" function, we constructed forest plots to visualize the relationship between DSCC1 expression in each cancer type and patient prognosis. Additionally, the details of 25 cohorts obtained from the PrognoScan (http://www.prognoscan.org/) database were used for external validation.

2.3. Genomic alteration and genomic instability analysis of DSCC1

The cBioPortal platform (https://www.cbioportal.org/) provides free access to the interactive exploration of cancer genomics data. It has the options "cancer types summary" and "mutations," which allowed us to systematically analyze the DSCC1 alteration frequency, types, and sites in the pan-cancer cohort. Particularly, the "survival" section under the "comparison/survival" module enables a detailed comparison of survival outcome differences between the DSCC1-altered and DSCC1-unaltered groups. This analysis included four indicators of survival endpoints: OS, DSS, PFI, and disease-free survival.

The copy number variation (CNV) dataset of all TCGA samples was downloaded from the GDC (https://portal.gdc.cancer.gov/) portal and processed using GISTIC software. The Kruskal–Wallis rank sum test was used to calculate DSCC1 expression differences among groups.

Using the data of tumor mutational burden (TMB), microsatellite instability, homologous recombination deficiency (HRD), loss of heterozygosity (LOH), mutant-allele tumor heterogeneity (MATH), neoantigens (NEO), DNA stemness score (DNAss), and RNA stemness score levels, we systematically analyzed the correlation between DSCC1 expression and genomic instability in the pan-cancer analysis through Spearman's correlation.

2.4. Gene set enrichment analysis

The gene set enrichment analysis (GSEA) was performed to explore significantly and differentially expressed pathways between the DSCC1 high- and low-expression groups in selected cancer types. Gene sets in the "C2.cp.v7.2.symblos.gmt [Curated]" collection from the MSigDB were used for analysis; the repetition times for each procedure were "5000," and the Benjamini–Hochberg procedure was used to adjust the p-value. The R package "ClusterProfiler" function was used to perform GSEA.

2.5. Correlation between DSCC1 expression and tumor immunity

The "Subtype" module of the TISIDB enabled us to visualize DSCC1 expression in different immune subtypes in the pan-cancer analysis. TIMER2.0 (http://timer.comp-genomics.org/) provides free access to explore gene expression and tumor immune infiltration in TCGA cohorts. Referring to previous research, we assessed the correlation of DSCC1 expression with myeloid-derived suppressor cells (MDSCs) and natural killer (NK) T cells (NKT/T cell NK) infiltration levels under the "immune" module [10]. Additionally, the single-sample GSEA algorithm, with gene sets consisting of markers of individual immune cells, enabled us to estimate the correlation of DSCC1 with the infiltration of 24 types of tumor-infiltrating lymphocytes (TILs) [11]. The Spearman correlation of DSCC1 expression with immunoregulatory genes (including immunostimulators, immunoinhibitors, major histocompatibility complex [MHC] molecules, chemokines, and chemokine receptors) was calculated, and the results were presented as heatmaps.

2.6. Correlation of DSCC1 expression with immune checkpoint blockade treatment response

BEST (https://rookieutopia.com/app_direct/BEST/) and TIDE (http://tide.dfci.harvard.edu/) are two platforms that provide information about immunotherapy for patients with cancer [12]. We evaluated the association of DSCC1 expression with the immunotherapy response and prognosis in the Dizier cohort 2013 melanoma MAGE, Riaz2018

melanoma PD-1/CTLA-4 cohort, Cho cohort 2020 advanced solid tumors PD-1/PD-L1, IMvigor210 PD-L1 BLCA cohort, Lauss2017 CAR-T melanoma cohort, Nathanson2017 CTLA-4 melanoma cohort, and Liu2019 PD-1 melanoma cohort. We also compared the predictive power between DSCC1 expression and other published biomarkers for immune therapy response. Moreover, the T-cell dysfunction degree was evaluated between DSCC1 high- and low-expression groups under the "expression" module.

2.7. Statistical analysis

For statistical analysis of the collected data, R software (v4.2.1) was used. The R package "ggplot2" function (v3.3.6) was used to visualize and display data. Using the Wilcoxon rank sum test and Wilcoxon signed rank test, we compared DSCC1 mRNA expression of tumor tissues with unpaired and paired normal controls, respectively. For DSCC1-related prognostic analysis, the *P*-value was determined using the Cox proportional hazards model and the log-rank model, from which the hazard ratio and 95% confidence intervals were derived. The Spearman correlation coefficient was calculated to assess the correlation between the two datasets. Statistical significance was assumed when the *P*-value was less than 0.05.

3. Results

3.1. Protein topology, subcellular localization, single-cell variation, and expression under physiological conditions

The results of the protein topology analysis revealed the intracellular membrane localization of DSSC1 under physiological conditions (Figure 1A). Using the indirect immunofluorescence assay to further characterize the subcellular location of DSCC1, we investigated DSCC1 distribution in the endoplasmic reticulum (ER), nucleus, and microtubules of human epidermal squamous cells (A-431), human malignant glioma cells (U-251 MG), and human osteosarcoma cells (U-2 OS). The colocalization between DSCC2 expression and the markers of the nucleus suggested a nuclear subcellular localization of DSCC1. By contrast, the DSCC1 protein did not overlap with the markers of ER and microtubules (Figure 1B). Additionally, we discovered that DSCC1 was widely expressed in normal tissues. In particular, EBV-transformed lymphocytes had the highest DSCC1 mRNA expression, whereas whole-blood samples had the lowest expression (Figure 1C). In the U-2 OS cell line, single-cell RNA sequencing using a fluorescent ubiquitination–based cell cycle indicator system showed a correlation of DSCC1 mRNA expression with the cell cycle phase (Figure 1D). The peak phase of DSCC1 expression was the S phase, followed by the S and G2 phases, and then the G1 phase. Protein-protein interaction (PPI) analysis showed that proteins that may interact with DSCC1 included CHTF18, RFC5, POLA1, RFC4, RFC3, CHTF8, TIPIN, WDHD1, RFC2,and PRIM1 (Figure 1E). It was also worth noting that DSCC1 expression was associated with body measurements, the presence of cancer or benign tumor, endocrine diseases, cardiovascular diseases, and gastrointestinal diseases, as suggested by the gene-disease interaction network analysis (Figure 1F). To conclude, we presented a comprehensive description of DSCC1 expression under physiological conditions using multi-omics data.

3.2. Transcriptomic patterns of DSCC1 in pan-cancer

To assess the transcriptomic patterns of DSCC1, we used data from the TCGA and GTEx databases to assess DSCC1 expression. Overall, DSCC1 mRNA expression levels were universally elevated in most tumors when compared with those in their corresponding normal controls. A comparison between tumor tissues and unpaired normal control tissues suggested that DSCC1 was overexpressed in tumors including BLCA, BRCA, CESC, CHOL, COAD, DLBC, ESCA, GBM, HNSC, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, OV, PAAD, PRAD, READ, SKCM, STAD, TGCT, THYM, UCEC, and UCS (abbreviations for the 33 types of cancer are shown in Figure 2). By contrast, DSCC1 expression in KICH, LAML, and THCA was lower than that in their normal controls (Figure 2A). Among the paired tumor tissues and para-tumor tissues of 16 cancers evaluated, patients with BLCA, BRCA, CHOL, COAD, ESCA, HNSC, KIRC, KIRP, LIHC, LUAD, LUSC, PRAD, READ, STAD, and UCEC had significantly higher DSCC1 expression (Figure 2B). We next evaluated the association of DSCC1 expression with tumor stages and grades. In tumor stage–relevant analysis, DSCC1 expression was positively correlated with pathological stages in ACC, BRCA, KICH, KIRC, KIRP, LUAD, LUSC, and UCEC (Figure 2C). Upregulated DSCC1 expression was observed in higher histological grades in CESC, HNSC, KIRC, LGG, LIHC, and UCEC. However, DSCC1 showed a negative correlation with the grades of STAD (Figure 2D). In summary, DSCC1 was generally highly expressed in tumor tissues and positively correlated with the grades and stages of some tumors, sug-

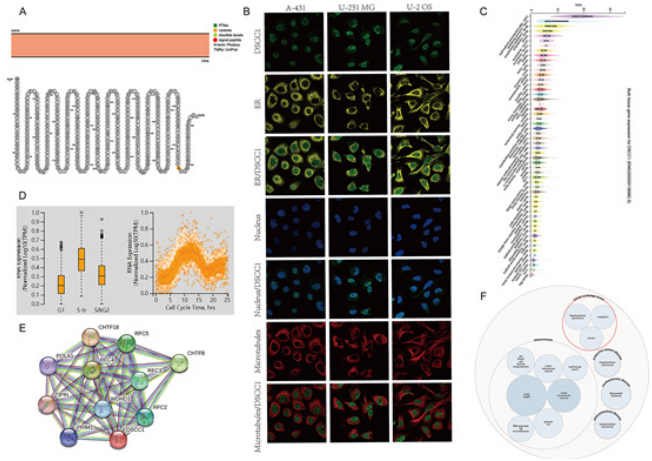

Fig. 1. Protein topology, subcellular location, PPI network, and transcriptional expression of DSCC1 in normal tissues under physiological conditions. (A) Protein topology of DSCC1 according to the Protter database. (B) Immunofluorescence staining analysis to determine the subcellular localization of DSCC1 in human epidermal squamous cells (A-431), human malignant glioma cells (U-251 malignant glioblastoma), and human osteosarcoma cells (U-2 osteosarcoma) according to the human protein atlas database. (C) Violin plot showing DSCC1 mRNA expression in human organs according to the GTEx database. (D) Plot showing the relationship between DSCC1 mRNA expression and cell cycle progression with single-cell RNA sequencing data in the U-2 osteosarcoma cell line. (E) PPI interaction network of DSCC1 according to the String database. (F) Identification of DSCC1-associated diseases from the Open Targets platform. DSCC1, DNA replication and sister chromatid cohesion 1; GTEx, Genotype-Tissue Expression; PPI, protein-protein interaction.

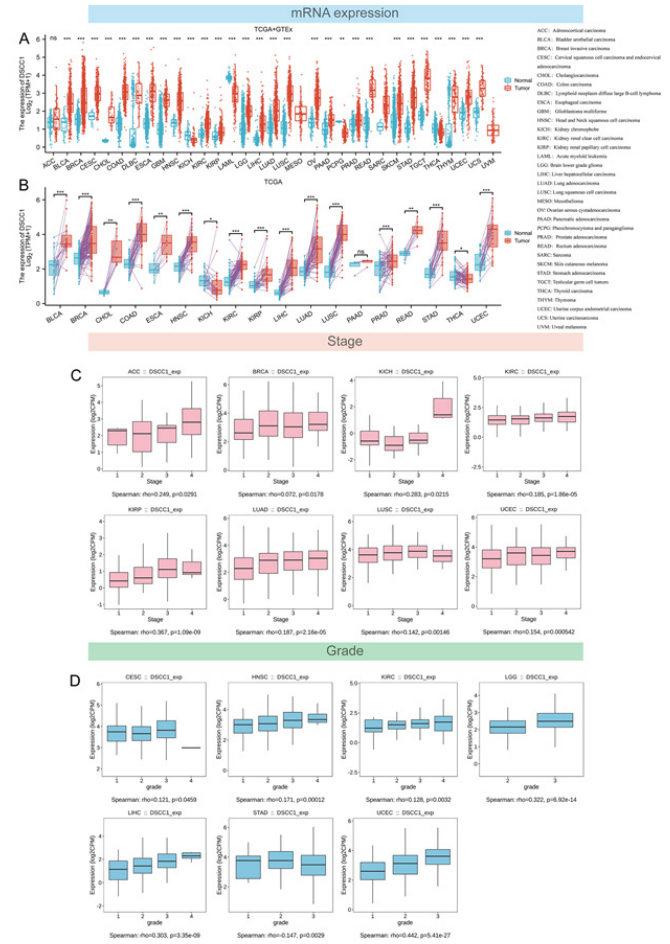

Fig. 2. Expression profile of DSCC1 in the pan-cancer analysis. DSCC1 mRNA expression in tumor tissues compared with that in unpaired (A) and paired normal tissues. (B) Association between DSCC1 expression and tumor stages in ACC, BRCA, KICH, KIRC, KIRP, LUAD, LUSC, and UCEC. (C) Association between DSCC1 expression and tumor grades in CESC, HNSC, KIRC, LGG, LIHC, STAD, and UCEC. *P<0.05; **P<0.01; ***P<0.001; ns, not statistically significant. DSCC1, DNA replication and sister chromatid cohesion 1. (D) DSCC1 shows a negative correlation with the grades of STAD.

gesting that DSCC1 might be involved in the progression of these tumors.

Furthermore, we evaluated the DSCC1 protein levels in the pan-cancer analysis based on HPA data. The results suggested that in nearly half of the tumor types observed, patients' tissues had predominantly high or medium intensity staining for the DSCC1 protein (Figure S1A). The DSCC1 proteomics expression was compared between tumor and normal tissues in COAD (Figure S1B), HNSC (Figure S1C), LIHC (Figure S1D), LUAD (Figure S1E), OV (Figure S1F), and UCEC (Figure S1G), and we observed higher DSCC1 protein expression in these tumors. From their corresponding immunohistochemical images, we observed deeper staining intensity of the DSCC1 protein in the tumor tissues.

3.3. Prognostic and diagnostic values of DSCC1 in pan-cancer

To learn more about whether DSCC1 affected the prognosis of patients with cancer, we conducted a survival analysis using two methods. From the heatmap displayed in Figure 4A, we found that DSCC1 was a potential pan-cancer prognostic biomarker. Overall, considering all survival indicators (OS, DSS, and PFI) and the two different methods of survival analysis, we considered that high DSCC1 expression was a risk factor for patients with ACC, BRCA, KICH, KIRP, LGG, LIHC, LUAD, MESO, PAAD, SARC, UCEC, and UCS. However, in ESCA and OV, higher DSCC1 expression was linked to longer patient survival time (Figure 3A). Additionally, the survival information of 25 independent GEO cohorts was used for external validation. From the image displayed in Figures 3B and C, we found that high expression of DSCC1 was still detrimental to the prognosis of patients with different cancers including BLCA, SARC, melanoma, osteosarcoma, lung cancer, BRCA, blood cancer, brain cancer, and eye cancer. These results suggested that elevated DSSC1 levels in most cancers were associated with poorer patient prognosis, suggesting that DSCC1 might play an oncogenic role in many cancers.

The diagnostic value of DSCC1 was also assessed. Among all 31 types of cancer observed, the area under the

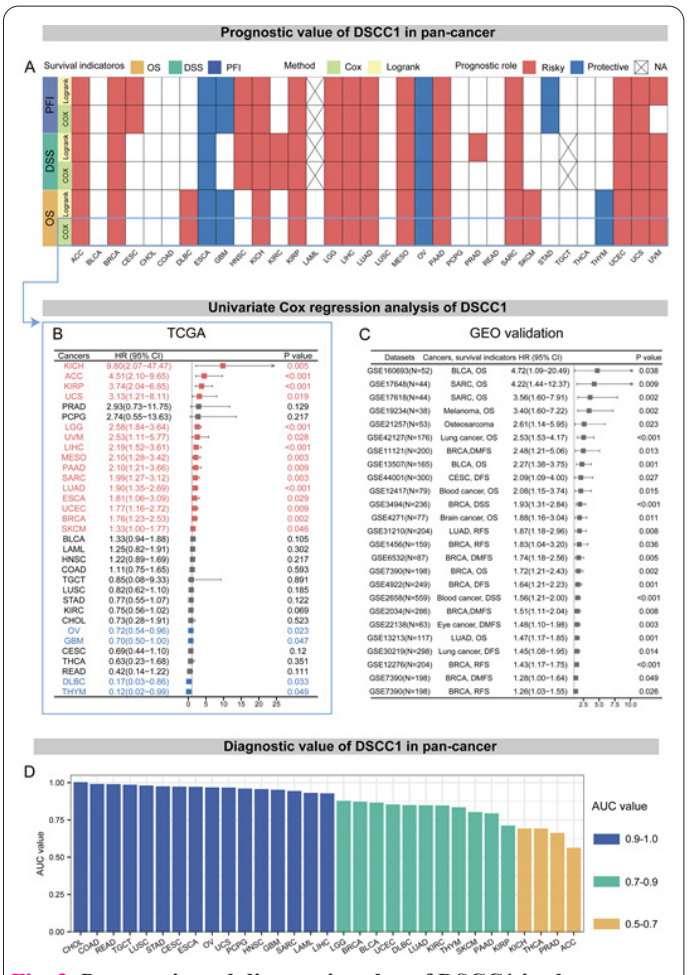

Fig. 3. Prognostic and diagnostic value of DSCC1 in the pan-cancer analysis. (A) Association between DSCC1 expression and overall survival, disease-specific survival, and progression-free interval according to univariate Cox regression and Kaplan-Meier analysis. This Fig. shows only results with P-values of <0.05. (B) The forest plot demonstrates the prognostic value of DSCC1 in cancers assessed by univariate Cox regression. The results with significant differences have been highlighted. (C) The prognostic value of DSCC1 is validated in 25 external independent Gene Expression Omnibus datasets. (D) Diagnostic value of DSCC1 in the pan-cancer analysis. The Y-axis indicates the AUC values of the ROC curves. Different colors indicate different ranges of AUC values. AUC, area under the curve; DSCC1, DNA replication and sister chromatid cohesion 1; ROC, receiver operating characteristic.

curve (AUC) values of the receiver operating characteristic (ROC) curves exceeded 0.9 in 16 cancers, indicating that DSCC1 had a high diagnostic value (AUC=0.9-1.0) in distinguishing these tumor tissues from their corresponding normal tissues (Figure 3D). Furthermore, DSCC1 had a moderate predictive value (AUC=0.7-0.9) in 11 cancers and a low predictive value (AUC=0.5-0.7) in 4 cancers.

3.4. Genomic alteration and genomic instability analysis of DSCC1 in tumors

Figure 4A illustrates DSCC1 genetic alteration profiles in pan-cancer cohorts of the TCGA database. From an overall perspective, the alteration frequency of DSCC1 exceeded 5% in 11 cancers, with genetic amplification being their predominant alteration type. We also identified that the highest frequency of DSCC1 genetic alteration appeared in OV, with the alteration frequency exceeding 20%. The types, sites, and number of cases of DSCC1 mutation are depicted in Figure 4B. We discovered that missense mutation was the primary DSCC1 mutation type, and X162_splice alteration, a splice mutation, was detected in one case of SARC and one case of LIHC (Figure 4C). The X162 site within the three-dimensional structure of the DSCC1 protein is shown in Figure 4B. We next evaluated the correlation between CNV and DSCC1 expression in pan-cancer. In most cancers evaluated, copy number gain was commonly characterized by higher DSCC1 expression levels than copy number neutral or loss (Figure 4D). To further examine whether there was an association between DSCC1 genomic alteration and patient prognosis in the pan-cancer cohort, we compared the difference in clinical outcomes between DSCC1-altered and -unaltered groups. The results showed that patients with DSCC1 alteration had significantly shorter disease-free survival duration (P<0.001) and progression-free survival time (P=0.005) than those without DSCC1 genomic alteration. Similarly, patients with DSCC1 alteration displayed inferior prognosis concerning DSS (P=0.468) and OS (P=0.637), while the results were not significant (Figure 4E). In summary, the genomic alterations of DSCC1 in pan-cancer were predominantly amplified and correlated with the prognosis of patients with cancer.

The relationships between DSCC1 and genomic instability indicators are shown in Figure S2. The results revealed that DSCC1 expression positively correlated with genomic instability in various cancers (Figure S2A). More precisely, DSCC1 expression was in accordance and significantly associated with most indicators in BLCA, BRCA, COAD, ESCA, HNSC, LGG, LUAD, LUSC, PRAD, SARC, and STAD. Noteworthy, DSCC1 significantly and negatively correlated with TMB, LOH, MATH, purity, and DNAss in THYM (Figure S2B). Collectively, these findings suggested that DSCC1 had a close relationship with genomic instability in pan-cancer, which, on the one hand, revealed the potential role of DSCC1 in cancer and, on the other hand, provided a new target for tumor therapy.

3.5. Gene set enrichment analysis of DSCC1 in cancers

To further investigate the biological processes in which DSCC1 was potentially involved in cancer, we conducted GSEA enrichment analysis in nine types of cancer, whose clinical outcome was significantly correlated with DSCC1 expression. The GSEA results are shown in Figures S3A-I. The most significantly enriched pathways in these tumors include cell cycle checkpoints, mitotic phases, polo-like kinase-mediated events, unwinding of DNA, Rho GTPase effectors, replication and pre-replication stress, DNA repair, and so on. These results disclosed a close association between DSCC1 and cell cycle, mitosis, and DNA replication and repair in various cancers.

3.6. Correlation between DSCC1 expression and immune subtypes in pan-cancer

By applying immunology-genomics methods, previous research identified and characterized six immune subtypes in the TCGA pan-cancer cohort, thus facilitating a better understanding of the association between the tumor immune microenvironment (TME) and disease outcomes [13]. We then investigated the DSCC1 expression pattern among different immune subtypes. We discovered that DSCC1 expression differed in six immune subtypes of the following cancers: BLCA, BRCA, COAD, ESCA, KIRP, LIHC, LUAD, LUSC, OV, PAAD, PRAD, READ, SARC, SKCM, and UCEC (Figure 5). To be specific, in ESCA, KIRP, LIHC, LUAD, PAAD, and PRAD, DSCC1 expression was higher in the wound-healing immune subtypes than in the other subtypes. For BLCA, BRCA, COAD, OV, READ, and UCEC, patients in the interferon-γ–dominant immune subtype had the highest DSCC1 expression. For LUSC, SARC, and SKCM, DSCC1 expression was the highest. Another interesting finding was that, among the six immune subtypes in all observed cancers, inflam-

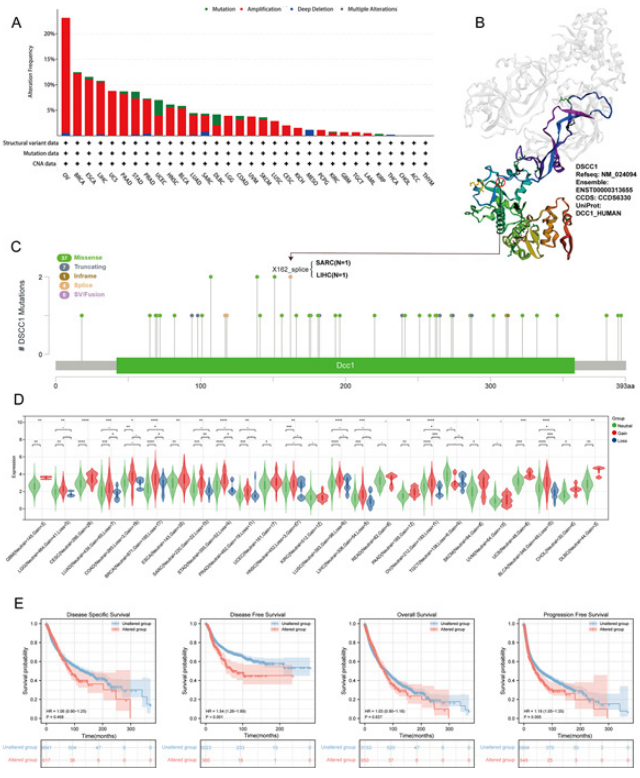

Fig. 4. Genomic alteration of DSCC1 in the pan-cancer analysis. DSCC1 alteration frequency (A) and mutation sites (C) are examined and exhibited in different cancer types. (C) The mutation site (X162) is displayed in the 3D structure of DSCC1. (D) Violin plot showing DSCC1 expression differences among the copy number neutral, loss, and gain groups in different cancer types. (E) Differences in prognostic outcomes (disease-specific survival, disease-free survival, overall survival, and progression-free survival) between the DSCC1-altered (red) and DSCC1-unaltered (blue) groups. *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001; –, not statistically significant.

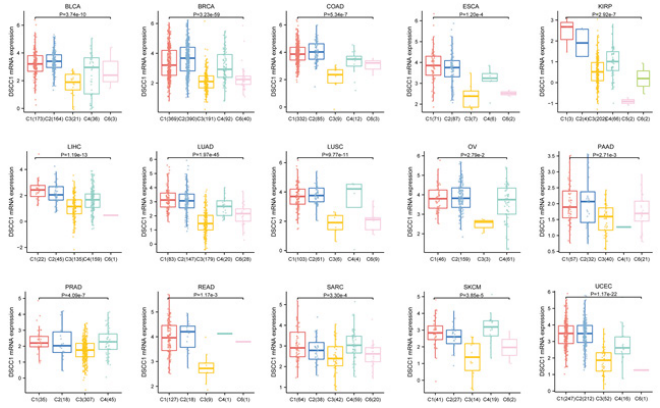

Fig. 5. DSCC1 is differentially expressed in distinct immune subtypes. C1: wound healing; C2: INF-γ dominant; C3: inflammatory; C4: lymphocyte depletion; C5: immunologically quiet; C6: TGF-β dominant. DSCC1, DNA replication and sister chromatid cohesion 1; INF-γ, interferon-gamma; TGF-β, transforming growth factor beta.

matory subtypes had the lowest DSCC1 expression. These findings suggested that DSCC1 might be closely related to the TME composition.

3.7. Correlation of DSCC1 with MDSC and NK T-cell infiltration

To further explore the relationship between DSCC1 expression and TME, our subsequent study analyzed the association of DSCC1 expression level with MDSC and NK T-cell infiltration using the xCell algorithm. As indicated in Figure S4, a significant positive association existed between DSCC1 expression and MDSC infiltration, and a significant negative association existed between DSCC1 expression and NKT infiltration in most tumors. In particular, we selected the top seven types of cancer that showed the strongest correlation with MDSC and NKT infiltration. The results are displayed as representative scattergrams. We could visually observe that the same expression trend between DSCC1 expression and MDSC infiltration in ACC (Cor=0.726, *P*=3.71e-13), LUAD (Cor=0.661, *P*=2.82e-63), LIHC (Cor=0.648, *P*=2.06e-42), UCEC (Cor=0.629, *P*=1.06e-33), READ (Cor=0.577, *P*=1.01e-13), STAD (Cor=0.562, *P*=6.46e-33), and SARC (Cor=0.532, *P*=3.18e-19). However, a converse trend between DSCC1 expression and NKT cell infiltration in the following cancers: UVM (Cor=−0.687, *P*=5.38e-12), DLBC (Cor=−0.427, *P*=5.42e-03), SKCM (Cor=−0.382, *P*=2.73e-17), CHOL (Cor=−0.355, *P*=3.62e-02), LUAD (Cor=−0.350, *P*=1.16e-15), BRCA-Basel (Cor=−0.349, *P*=2.4e-06), and SARC (Cor=−0.304, *P*=1.32e-06). These observations illustrated that DSCC1 was putatively associated with the extent of tumor immune cell infiltration, which might play a key role in immune-oncology interactions.

3.8. Correlation between DSCC1 expression and tumor immune landscape

We next evaluated the association of DSSC1 with TILs and immunoregulatory genes to gain a better understanding of the correlation between DSCC1 expression and the pan-cancer tumor immune landscape. As depicted in Figure S5A, a positive correlation existed between DSCC1 expression and the infiltration of Th2 and T helper cells. By contrast, in most instances, particularly in GBM, LUAD, LUSC, SARC, SKCM, TGCT, and UCEC, DSCC1 expression was inversely linked to the immune infiltration of other lymphocytes (Figure S5A). DSCC1 expression was negatively correlated with the immune infiltration of other lymphocytes in most cases, especially in GBM, LUAD, LUSC, SARC, SKCM, TGCT, and UCEC (Figure S5A). Interestingly, DSCC1 expression was positively correlated with most immunostimulators in the pan-cancer analysis, and this condition was more prominent in patients with KICH, KIRC, KIRP, LGG, LIHC, THCA, and UVM (Figure S5B). The relationship between DSCC1 expression and immunoinhibitors was also estimated. Of all 24 immunoinhibitors evaluated, DSCC1 was significantly associated with more than half of the immunoinhibitors in cancers including ACC, BLCA, BRCA, GBM, KIHC, KIRC, KIRP, LGG, LIHC, LUSC, PCPG, SARC, SKCM, TGCT, THCA, THYM, and UVM (Figure S5C). Additionally, DSCC1 was negatively correlated with most of the MHC molecules in GBM, LUAD, LUSC, SARC, SKCM, THYM, and UCEC and positively correlated with most of the MHC molecules in KIRC, LGG, LIHC, PAAD, PCPG, and UVM (Figure S5D). Most chemokines in COAD, KICH, KIRC, LIHC, and THCA were significantly positively correlated with DSCC1 expression. However, negative correlations were observed in GBM, LUSC, SARC, TGCT, and THTM (Figure S5E). Similarly, DSCC1 expression was correlated with various chemokine receptors in pan-cancer analysis, especially in GBM, KICH, KIRC, KIRP, LGG, LIHC, LUAD, LUSC, SARC, TGCT, THCA, and THYM (Figure S5F). Overall, these results implied that DSCC1 might be closely related to tumor immunity.

3.9. Association between DSCC1 and immune checkpoint blockade response

To make DSCC1 more clinically applicable, we explored the relationship between DSCC1 expression and immune checkpoint blockade (ICB) response in the pan-cancer analysis. First, we assessed the DSCC1 expression differences between nonresponders and responders among patients receiving ICB treatment. Our analysis showed that patients who responded to ICB therapy had significantly lower DSCC1 expression in the DiZier cohort (*P*=0.023), Riaz cohort (*P*=0.042), and Cho cohort (*P*=0.027). By contrast, those responding better to ICB treatment had high DSCC1 expression in the IMvigor210 cohort (*P*=0.0037) (Figure S6A). The relationship of DSSC1 expression with patient survival endings after ICB treatment was also assessed. Patients with lower DSCC1 expression in the Lauss cohort (*P*=0.028), Cho cohort (*P*=0.013), Nathanson cohort (p=0.028), Liu 2019 cohort (*P*=0.017), and Riaz2017 (*P*=0.003) cohort had prolonged survival duration (Figure S6C). However, in the IMvigor210 cohort, patients with high DSCC1 expression had better OS probability (*P*=0.037; Figure S6C), which also corresponded to the differential expression of DSCC1 depicted in Figure S6A. Moreover, the performance of DSCC1 in predicting ICB outcome was calculated and compared with that of some existing biomarkers. Our study indicated that DSCC1 obtained higher predictive values (AUC>0.5) in 9 of the 20 cohorts evaluated. In the study of "Uppaluri2020, PD-1 HNSC" (AUC=0.72), DSCC1 showed higher predictive accuracy than other existing biomarkers (Figure S6B). We also assessed the relationship between DSCC1 expression and cytotoxic T lymphocyte (CTL) dysfunc-

tion. We discovered that DSCC1 expression significantly and positively correlated with CTL dysfunction in the observed six cancers: LIHC (z=2.32, *P*=0.020), melanoma (z=2.54, *P*=0.011), HNSC (z=2.83, *P*=0.005), BRCA (z=3.14, *P*=0.002), COADREAD (z=3.33, *P*=0.001), and GBM (z=2.54, *P*=0.011). CTL infiltration showed a positive association with patient survival outcomes in these cancers when DSCC1 expression was weak. By contrast, high DSCC1 expression seemed to attenuate or even reverse the prognosis-protective role of CTL (Figure S6D). Consequently, these observations collectively suggested that DSCC1 was a potential predictive biomarker for tumor immune therapy. High DSCC1 expression might exacerbate CTL dysfunction, thus affecting the effectiveness of immunotherapy and patient prognosis.

4. Discussion

In the current research, we first explored the physiological dimension of DSCC1. We observed that DSCC1 had an intracellular membrane localization, with the nucleus being the specific localization site. Additionally, PPI analysis demonstrated that the proteins RFC2-5, CHTF8, and CHTF18 were Likely to interact with DSCC1. These results were consistent with the previously reported structure of the CTF18-RFC complex [14], and the nuclear positioning of the DSCC1 protein also corresponded to its involvement in DNA replication. Moreover, the peak expression of DSCC1 in the S phase observed in this study was associated with the S phase activation in the cell cycle checkpoint and PCNA-loading activity [15, 16]. DSCC1-associated disease predicted from the Open Targets platform suggested that DSCC1 might be related to cancer or benign tumor occurrence. Indeed, RFC is actively involved in tumorigenesis and contributes to various malignant behaviors of tumor cells, such as proliferation, progression, invasion, and metastasis [17]. We found that other proteins predicted in our PPI analysis, namely, POLA1, PRIM1, and WDHD1, were all related to DNA synthesis and were associated with the development of human malignancies. In our subsequent expression analysis, we observed generally upregulated transcriptomic levels of DSCC1 in tumor tissues, which partly reflected the abnormally active state of DNA synthesis in tumor tissues. Moreover, in some tumors, DSCC1 expression increased with increasing grading stage, suggesting that DSCC1 might be closely associated with the progression of these tumors. In conclusion, these findings provoked our research group to further investigate the role of DSCC1 in cancer.

DSCC1 expression–based survival analysis in our study demonstrated that, in many types of cancer, including ACC, BRCA, KICH, KIRP, LGG, LIHC, LUAD, MESO, PAAD, SARC, UCEC, and UVM, patients with higher DSCC1 expression tend to have a poorer prognosis. Wang *et al*. [9] revealed that DSCC1 mRNA expression not only significantly increases in BRCA tissues and cell line (MCF-7) but also varies among different molecular subtypes, which indicated that DSCC1 overexpression probably plays a role in BRCA progression. For colorectal cancer, DSCC1 is a potential downstream target of E2F1 and is tightly associated with the growth and metastasis of colon cancer cells [7]. In HCC, DSCC1 is overexpressed in HCC tumor tissues and linked to decreased patient survival time. DSCC1 knockdown triggers significant cell cycle arrest and inhibits HCC cell proliferation [8]. Additionally, a bioinformatics approach–based study confirmed that DSCC1 is an independent prognostic biomarker in LUAD [18]. Consistent with the above research, the correlation between higher DSCC1 expression and worse patient prognosis in BRCA, LUAD, and LIHC has been reported in the present study. We also observed increased DSCC1 expression with prolonged survival time in patients with ESCA and OV, which suggested that there might be heterogeneity regarding the role of DSCC1 in tumors. To conclude, our findings that patients with high DSCC1 expression had a worse prognosis in most cancers paved the way for future studies of DSCC1 in many other tumors of neurological (LGG), genitourinary (ACC, KICH, KIRP, UCEC, and UCS), digestive system (PAAD), and mesenchymal origins (SARC and MESO).

Our subsequent analysis revealed a predominantly amplified genomic alteration of DSCC1 in the pan-cancer analysis. Moreover, after a systematic evaluation between DSCC1 expression and different CNV types, we found that DSCC1 expression was generally higher in the copy number gain group than in the other groups. Likewise, we observed shorter survival times in the DSCC1-altered group (amplification accounted for most cases), and this difference was significant in the DSS and progression-free survival analysis. These observations indicated the prevalence of DSCC1 amplification in human tumors and supported our previous observation that patients with high DSCC1 expression usually had a worse prognosis. CNV in cancers is an important approach to the regulated expression of respective genes and proteins, thereby increasing the expression of oncogenes and either enhancing its function or silencing the gatekeeper function of tumor-suppressive genes [19]. Considering its important role in DNA synthesis, we hypothesize that the genomic alteration of DSCC1 observed in the pan-cancer analysis might facilitate tumor growth. Another noteworthy point is that the DSCC1 gene is located at 8q24 on the human chromosome, a region that is most frequently amplified and is correlated with the risk of human malignancy [8]. The MYC gene, one of the most well-studied oncogenes, is also located on the 8q24 region of the chromosome. We noticed that DSCC1 is located on the same chromosome as that of MYC and is commonly amplified in cancer, which partly explains the universal upregulation of DSCC1 expression in tumor tissues, on the one hand, and suggests a possible functional similarity to MYC, on the other hand.

Furthermore, the present study revealed a previously unrecognized association between DSCC1 expression and genomic instability. Genomic instability, which refers to the increased tendency of cells to acquire genomic alterations, has long been considered a hallmark of cancers [20]. Genomic instability is a key contributor to intratumor heterogeneity, and recent studies have tightly linked genomic instability to clinical outcomes, therapy resistance, and disease progression in patients with cancer [21]. It was intriguing that, in most cancers, DSCC1 expression was positively correlated with genomic instability indicators, especially in HRD and LOH. Cancers exhibiting high HRD are more sensitive to poly (ADP ribose) polymerase inhibitors (PARPi), which induce lethal DNA lesions to tumor cells, thereby exerting their antitumor effects [22]. LOH is a common genetic event in tumor development and is regarded as a therapeutic option for precision medicine in patients with cancer [23]. Collectively, HRD and

LOH are therapeutically relevant biomarkers for predicting treatment response to PARPi among patients with cancer [24]. In our study, we found that DSCC1 positively and significantly correlated with HRD and LOH in various cancers including BLCA, BRCA, COAD, HNSC, KIRP, LGG, LIHC, LUAD, LUSC, MESO, OV, PAAD, PRAD, SARC, STAD, and UCEC. Therefore, we hypothesized that screening cancer patients for PARPi sensitivity based on their DSCC1 expression levels would decrease drug-related toxicities, and thus, patients with cancer would better benefit from targeted therapies.

In the GSEA analysis performed in the present study, DSCC1 was found to be probably involved in some biological processes, namely, cell cycle checkpoints, mitotic phases, polo-like kinase-mediated events, Rho GTPase effectors, and DNA repair, which might influence the prognosis of patients with cancer. Cell cycle checkpoints decelerate cell cycle progression, avoid the accumulation and transmission of genetic errors during cell division, and induce cell cycle exit and cell death promptly [25]. Similarly, the mitotic phase is essential for the even distribution of the genetic material to identical daughter cells. Anti-mitotic agents, a vital cancer treatment approach, disturb mitosis in tumor cells, trigger mitotic arrest, and eventually result in cell death [26]. Another noteworthy point is that DNA repair is fundamental to maintaining genomic integrity and stability. DNA repair defects make cancer cells more vulnerable to DNA damage, thereby fueling tumorigenesis [27]. Moreover, polo-like kinase is identified as a major regulator of cell cycle progression and a key contributor to carcinogenesis [28]. Recently, their previously unrecognized function in regulating DNA repair has also been revealed [29]. The processes described above are inherently closely related. These findings indicate that DSCC1 might be involved in these important processes and thus influence tumor progression. However, only a few studies have investigated how DSCC1 specifically functions in tumors through these processes, and our GSEA analysis may be useful in guiding further studies.

The immune cells not only infiltrate tumors but also evolve and antagonize with cancer cells, thereby affecting tumor growth and spread [30]. However, to the best of our knowledge, there is very limited research on DSCC1 in tumor immunity. Therefore, we subsequently explored the association of DSCC1 with different immune subtypes, tumor immune cell infiltration, and immunomodulatory genes in the pan-cancer analysis. Surprisingly, DSCC1 expression was the lowest in the C3 immune subtype in most tumors, whereas a previous study demonstrated that this subtype was associated with the best prognosis in cancer across all six subtypes [13], suggesting that the effect of DSCC1 on tumor patient prognosis may have been due, partly, to an influence on tumor immune cell infiltration. This result was confirmed from our subsequent observations in the present study that DSCC1 expression was correlated with the extent of infiltration of tumor immune cells. DSCC1 correlated with the immune infiltration of MDSC in most cancers assessed in the present study, and on the contrary, it was negatively correlated with NKT infiltration. Furthermore, a significant correlation existed between DSCC1 with TIL infiltration and many immunoregulatory genes. These results collectively suggested that DSCC1 might be closely associated with the TME and that, in most cases, DSCC1 might mediate tumor immune escape. In this discussion, we found that DSCC1 and genetic instability were closely related to each other, and the latter enables the tumor cells to eschew deleterious immune activation, partially because of the direct interference with antigen presentation [31]. However, the mechanism by which DSCC1 exactly affects the TME needs to be investigated in more detail.

ICB therapy has recently had unprecedented progress in cancer treatment. It can reinvigorate anticancer immunity and play a pivotal role in tumor treatment [32]. As DSCC1 and tumor immune cell infiltration are closely related, as discussed in this study, we then investigated the effect of DSCC1 on tumor immunotherapy. We found that, except for BLCA, patients with low DSCC1 expression in the observed cancers responded better to immunotherapy and had more prolonged survival after immunotherapy. Moreover, DSCC1 expression is related to the function of CTL. CTL can perform its function better in patients with cancer who have low DSCC1 expression and prolong patient survival time. We hypothesized that the poor response of patients with high DSCC1 expression might have been due to high levels of DSCC1 causing CTL dysregulation, which, in turn, limited the T-cell function that would otherwise be enhanced after ICB treatment [33]. These findings might add to its potential to promote tumor immune escape. However, in immunotherapy of BLCA, we observed a contrasting result, suggesting that DSCC1 affects the TME in a heterogeneous manner. Whether targeting DSCC1 can restore CTL cell dysfunction and thus enhance the efficacy of immunotherapy needs to be validated in further large-scale clinical trials.

The present study had limitations, which should be considered. First, most of the findings were based on an analysis of public databases and required subsequent validation in numerous clinical and cellular experiments. Second, given the important function of DSCC1 in normal cells, targeting DSCC1 treatment in tumor cells may have side effects; therefore, precisely targeted treatment of DSCC1 expression, as with the successful use of other mitotic inhibitors such as Aurora kinase inhibitors, to inhibit tumor growth while avoiding the effect on normal tissues, needs to be studied in a detailed manner.

5. Conclusion

To the best of our knowledge, this study is the first to comprehensively characterize the oncogenic and immunological roles of DSCC1 in human cancers. First, we found that DSCC1 expression was commonly upregulated in cancer and negatively correlated with the prognosis of patients with cancer. We then revealed that DSCC1 was commonly amplified in tumors and associated with genomic instability. DSCC1 might influence the cell cycle, DNA repair, and other processes and consequently contribute to tumor progression. Finally, we found that DSCC1 was closely correlated with TME and could be utilized as a potential biomarker in predicting immunotherapy efficacy. The main findings of this work are illustrated in Figure S7. In conclusion, DSCC1 is a novel target for cancer therapy, and targeting DSCC1 may be a promising therapeutic approach for tumor management.

Authors' contributions

HlL: conception and design. ZwC and LhW: formal analysis. RlW: visualization. LjW, FyC, and RmP: writing and

revision of the manuscript. XyY: funding acquisition and study supervision. All authors read and approved the final manuscript.

Consent for publications
All authors have read and approved the final manuscript for publication.

Ethics statement
Not applicable.

Acknowledgments
We are very grateful for the publicly available databases mentioned in the materials section. We thank Bullet Edits Limited for linguistic editing and proofreading of the manuscript.

Funding
This research was supported by the fund of Project A of the First Affiliated Hospital of Xi'an Jiao Tong University (XJTU-2021-01).

Conflicts of interest
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Figures were created with the help of Figdraw (www.figdraw.com).

Data availability statement
This study analyzed publicly available datasets. These datasets are available from the websites mentioned in the "materials and methods" section.

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