Bioinformatics Analysis of IGSF9B Gene in Patients Diagnosed with Colorectal Carcinoma

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ABSTRACT

Cell adhesion molecules (CAMs) are involved in many cellular processes such as proliferation, apoptosis, metastasis and have the potential to be diagnostic markers and therapeutic targets for malignancies. This study aimed to investigate the role of the IGSF9B gene, a CAM, in colorectal carcinoma via bioinformatics databases. GEPIA2 was used for gene expression analysis, UALCAN for methylation analysis, Kaplan-Meier Plotter for prognosis analysis, cBio Cancer Genomics Portal for gene alteration analysis, and Tumor Immune Estimation Resource databases were used for correlation analyses. In colon adenocarcinoma (COAD) and rectum adenocarcinoma (READ) cohorts, IGSF9B gene expression was decreased compared to normal samples ($p< 0.05$). Hypermethylation was observed in the IGSF9B gene promoter region in the COAD cohort ($p< 10^{-12}$)) and hypomethylation was observed in the READ cohort ($p= 5.58x10^{-5}$). IGSF9B gene changes were observed in 36 out of 526 patients (7%). In COAD there was a significant weak positive correlation between IGSF9B gene expression and CD4+ T cells, macrophages, neutrophils, and dendritic cells infiltrations. In READ there was a significant weak positive correlation between IGSF9B gene expression and CD4+ T cells and dendritic cells infiltration. Low IGSF9B gene expression levels were associated with longer OS ($p= 0.0079$) and RFS ($1.8x10^{-6}$). Low expression of IGSF9B gene may be a positive prognostic marker in colorectal cancer patients. Also, alterations in IGSF9B gene may be effective in colorectal carcinogenesis.

Keywords: Cell adhesion molecules, IGSF9B gene, Colorectal carcinoma

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer-related deaths.[1] CRC is a very heterogeneous malignancy, and well-known genetic alterations and signaling pathway pathologies play a role in its pathogenesis.[2] The mechanism of CRC development focuses on chromosomal instability, CpG island methylator phenotype (CIMP), and microsatellite instability (MSI) pathways.[3,4] Adenomatous polyposis coli (APC) mutation, KRAS oncogene activation and TP53 tumor suppressor gene inactivation are well described in the chromosomal instability pathway, MGMT and MLH1 hypermethylation in the CIMP pathway and DNA mismatch repair gene defects in the MSI pathway.[4-7]

Although cell adhesion molecules (CAMs) are molecules that support the binding of cells to each other and ensure tissue integrity by establishing relationships with extracellular matrix elements, there are studies suggesting that their overexpression or underexpression plays a role in cancer pathogenesis, but the data are not clear.[8,9] CAMs not only connect cells to each other, but also function as receptors in the activation of various intracellular signaling pathways due to their structure.[10]

It has a role in the regulation of many cellular processes such as cell proliferation, cell differentiation, invasion, immunological function, apoptosis, metastasis.[11] Therefore, a change in CAM expression will affect cell and tissue behavior. Traditionally, CAMs are divided into four families: cadherins, selectins, integrins, and members of the immunoglobulin superfamily (IgSF).[12]

There are publications indicating that various CAMs can be diagnostic markers in different malignancies, and some CAMs can be therapeutic targets, especially in hematological malignancies and melanoma.[13-17] Studies on the role of CAMs in patients with CRC are quite limited. There are studies showing that the levels of Intercellular Adhesion Molecule 1 (ICAM-1) and P-Selectin are increased in patients with CRC and that the level of matrix metalloproteinase-7 is correlated with the tumor stage.[18-20] There are also a few studies showing a relationship between the decrease in ICAM-1 and P-Selectin levels and disease progression, but the relationship between these markers and microsatellite status and PD1-PDL1 levels, which are of significant importance in CRC treatment selection and prognosis, has not been examined.[21,22]

IGSF9, part of the IgSF family, was first cloned in 2000 and has been shown to be downregulated in malignant melanoma and colorectal familial polyposis and upregulated in gallbladder cancer, ovarian cancer, and endometrial cancer.[23-27] IGSF9B, a component of the same family, is a synaptic CAM and its dysfunction has been shown to be associated with psychiatric disorders and seizure development.[28] There are two studies in the literature examining the relationship between the disorder in the IGSF9B gene and cancer, both of which were bioinformatics studies involving breast cancer patients.[29,30] In these studies, it was found to be associated with shorter median overall survival (mOS).

Individualized treatments are becoming widespread in all types of cancer, including patients diagnosed with CRC, and CAMs may also be important in determining prognosis and treatment. In our study, we examined the relationship between CRC and the IGSF9B gene, which is a part of the IgSF family, using various bioinformatics databases.

MATERIALS AND METHODS

Gene Expression Analysis

The GEPIA (Gene Expression Profiling Interactive Analysis) web server is an important resource for gene expression analysis based on tumor and normal samples obtained from The Cancer Genome Atlas (TCGA) and Genotype-Tissue Expression (GTEx) databases. The updated and improved version of this database, GEPIA2 (http://gepia2.cancer-pku.cn/#index), has moved gene expression determination to the transcription level, allowing specific cancer subtype analysis and comparison between them.[31] For gene expression analysis, the "Expression DIY" tab was selected in the GEPIA2 database and then "Match TCGA normal and GTEx" data. The method for differential analysis is one-way ANOVA. |Log2FC| Cutoff: 1 and p-value cutoff: 0.05 were determined. There were 275 patients in the colon adenocarcinoma (COAD) cohort; 92 patients in the rectum adenocarcinoma (READ) cohort. In addition, the "Stage Plot" tab was used to analyze expression levels according to stages.

Validation of IGSF9B Gene Expression

The Human Protein Atlas database (https://www.proteinatlas.org/) was used for validation of IGSF9B gene expression at the protein level in CRC and normal colon tissues.[32,33]

DNA Methylation Analysis

This study used the open access UALCAN (https://ualcan.path.uab.edu/) database for DNA promoter methylation analysis. This platform uses TCGA DNA methylation data generated using the Illumina Infinium HumanMethylation450 BeadChip. These data are processed to calculate average methylation (beta) values for each gene, considering the CpG sites located in the promoter region of the gene.[34]

Survival and Prognosis Analysis

Kaplan-Meier (KM) Plotter (https://kmplot.com/analysis/) database was used for relapse free survival (RFS) and mOS analysis.[35] KM plotter gene expression data, RFS and overall survival OS information are downloaded from The Gene Expression Omnibus (GEO), European Genome-Phe-

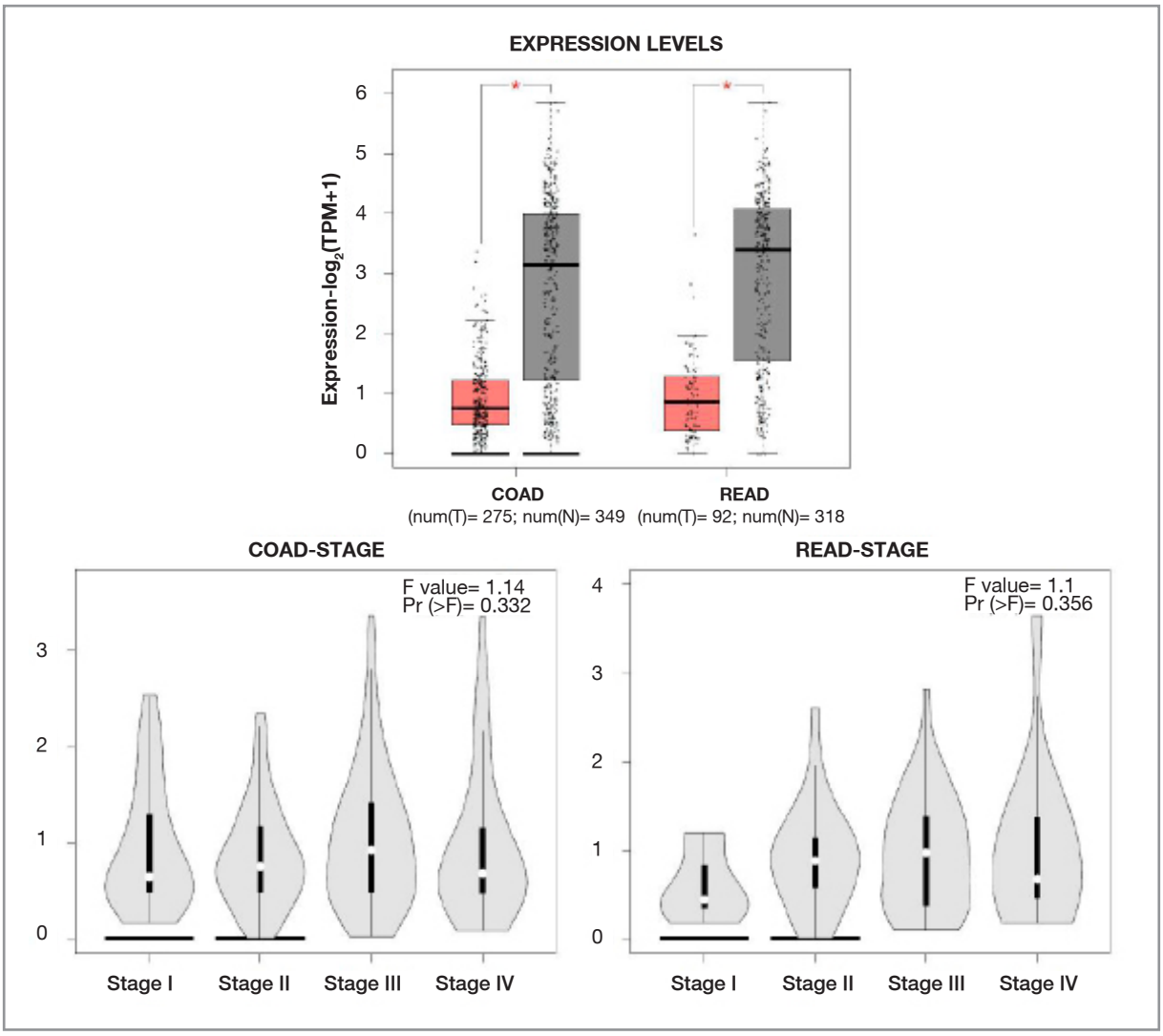

Figure 1. IGSF9B expression levels in normal and tumor samples in COAD and READ cohorts and changes in expression levels according to stages. COAD= Colon adenocarcinoma; READ= Rectum adenocarcinoma. *: p< 0.05. GEPIA2 database was used. T= Tumor; N= Normal.

nome Archive (EGA) and TCGA. In this platform, two cohorts are divided into low and high according to their expression levels. When comparing, significance is calculated using the Cox-Mantel (log rank) test. Hazard rate (HR) and False discovery rate (FDR) are calculated.[36] In this study; After entering IGSF9B, affymetrix id: 215166_at, Auto select best cutoff and only JetSet best probe set options were selected.[37] In the KM plotter database, there were 1336 patients for RFS analysis and 1061 patients for OS analysis in the colon cancer tab. Survival analysis was also performed according to cancer location. RFS analysis was performed on 365 patients in the proximal location and 545 patients in the distal location. OS analysis was performed on 308 patients in the proximal location and 491 patients in the distal location. p value < 0.05 was considered significant.

Gene Alteration Analysis

cBio Cancer Genomics Portal (https://www.cbioportal.org/) is an open access resource that allows interactive exploration of multidimensional cancer genomics datasets. Mutations, copy number alterations (CNA) are accessed on this platform. Genomic data of all patients can be summarized through a short graphical summary called OncoPrint. Mutation details are also provided on this platform.[38]

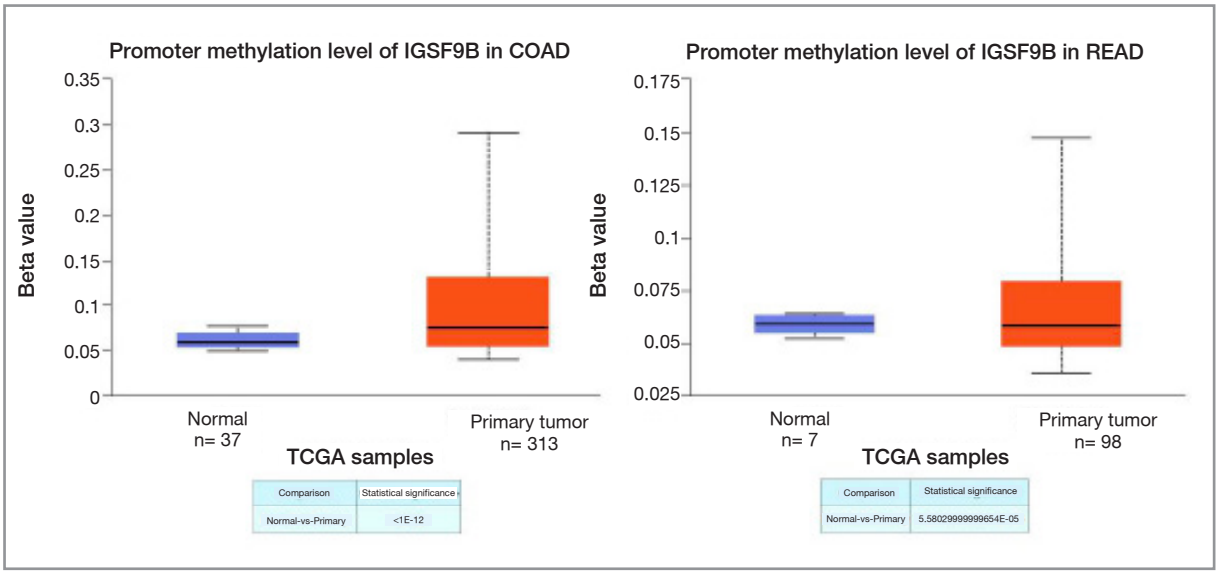

Figure 2. Promoter region methylation levels in the IGSF9B gene in normal and tumoral TCGA samples in the COAD and READ cohorts. COAD: Colon adenocarcinoma; READ: Rectum adenocarcinoma. Created using the UALCAN database.

For mutation analysis, 526 samples with mutation and CNA data from the Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) dataset were used in this platform.

Correlation Analysis of Gene Expression and Immune Infiltration/immune Checkpoint Inhibitors Targets

The "Gene" module in the Tumor Immune Estimation Resource (https://cistrome.shinyapps.io/timer/) web tool, which visualizes data, was used to detect the interaction between gene expression and tumor-infiltrating B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells. In addition, the "Correlation" module in this web tool draws the expression distribution graphs between the desired gene pair in the desired cancer type with Spearman correlation.[39] Thus, the correlation between IGSF9B gene expression levels and immune checkpoint inhibitors target genes PDCD1, CTLA4, CD274 expression levels were examined. There were 457 patients in the COAD cohort and 166 patients in the READ cohort.

Ethical approval: Since the data used in our study were obtained from TCGA and other public databases, ethical approval was not required.

RESULTS

Gene Expression Analysis Results

IGSF9B gene expression levels were significantly lower in tumor samples compared to normal samples in both COAD and READ cohorts ($p< 0.05$). In addition, there was no significant difference in IGSF9B gene expression levels between cancer stages in both cohorts (Figure 1).

DNA Methylation Analysis Results

In the IGSF9B gene promoter region, significantly higher methylation levels were found in the COAD cohort compared to normal samples (0.059 (Interquartile range (IQR): 0.055-0.069); in tumor samples, 0.075 (IQR: 0.056-0.13) ($p< 10^{-12}$). In the same gene region, in the READ cohort compared to normal samples (0.059 [IQR: 0.055-0.063]); Significantly lower methylation levels of 0.058 (IQR: 0.049-0.079) were found in tumor samples ($p= 5.58\times10^{-5}$) (Figure 2).

Survival and Prognosis Analysis Results

Low IGSF9B gene expression levels were associated with longer OS ($p= 0.0079$, FDR: over 50%). mOS was 112 months in the high expression cohort and 183 months in the low expression cohort. Low IGSF9B gene expression levels were associated

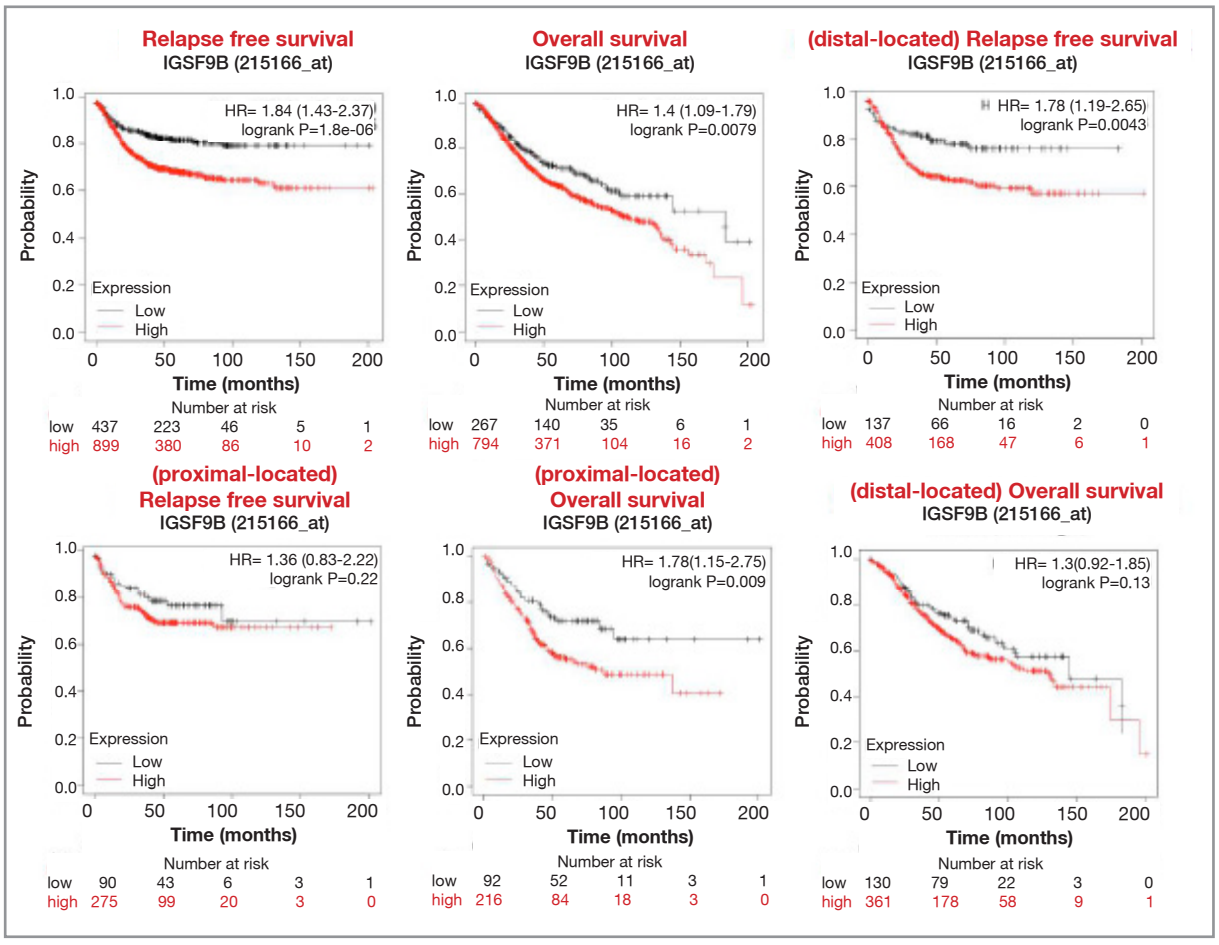

Figure 3. Overall survival and Relapse Free Survival curves according to different expression levels of IGSF9B gene in all COAD and READ cohorts and separately according to regional involvement. Curves were generated using https://kmplot.com/analysis/.

with longer RFS (P= $1.8x10^{-6}$, FDR: 1%). While improvement in RFS and OS was observed in the overall group with low IGSF9B gene expression level, when analyzed according to location, the improvement in RFS was statistically significant in patients with distal location (p= 0.0043, FDR: over 50%) and in OS in patients with proximal location (p= 0.009, FDR: over 50%) (Figure 3).

Gene Change Analysis Results

In the IGSF9B gene, changes were observed in 36 out of 526 patients (7%) (Figure 4). Gene changes according to cancer types: In the Mucinous Adenocarcinoma of the Colon and Rectum group, 5 out of 56 cases (8.93%) and all in the form of mutation; in the Colon Adenocarcinoma group, 29 out of 333 cases (8.71%) (27 cases with mutation and in 2 cases with Deep Deletion) and in the Rectal Adenocarcinoma group, 2 out of 137 cases (1.46%) and all in the form of mutation were detected (Figure 5).

Somatic mutation frequency was 6.5%. A total of 40 mutations were observed: 34 missense, 4 truncating (3 Frameshift ins, 1 Frameshift del), 1 inframe and 1 splice mutation. Driver mutations were not found in any of the patients, all were in the "unknown significance" category. Of the mutations, 1 frameshift ins (AA change Q147Pfs*10) and 1 frameshift del (AA change Q147Sfs*13) were on the I-set: Immunoglobulin I-set domain (140 - 225). The other 2 frameshift ins (AA change T1083Hfs*72) were outside the domains and were the same type of mutation observed in two different patients. Of the missense mutations, 1 was on I-set: Immunoglobulin I-set domain (140 - 225), 3 were on I-set: Immunoglobulin I-set domain (230 - 321), 4 were on Ig_2: Immunoglobulin domain

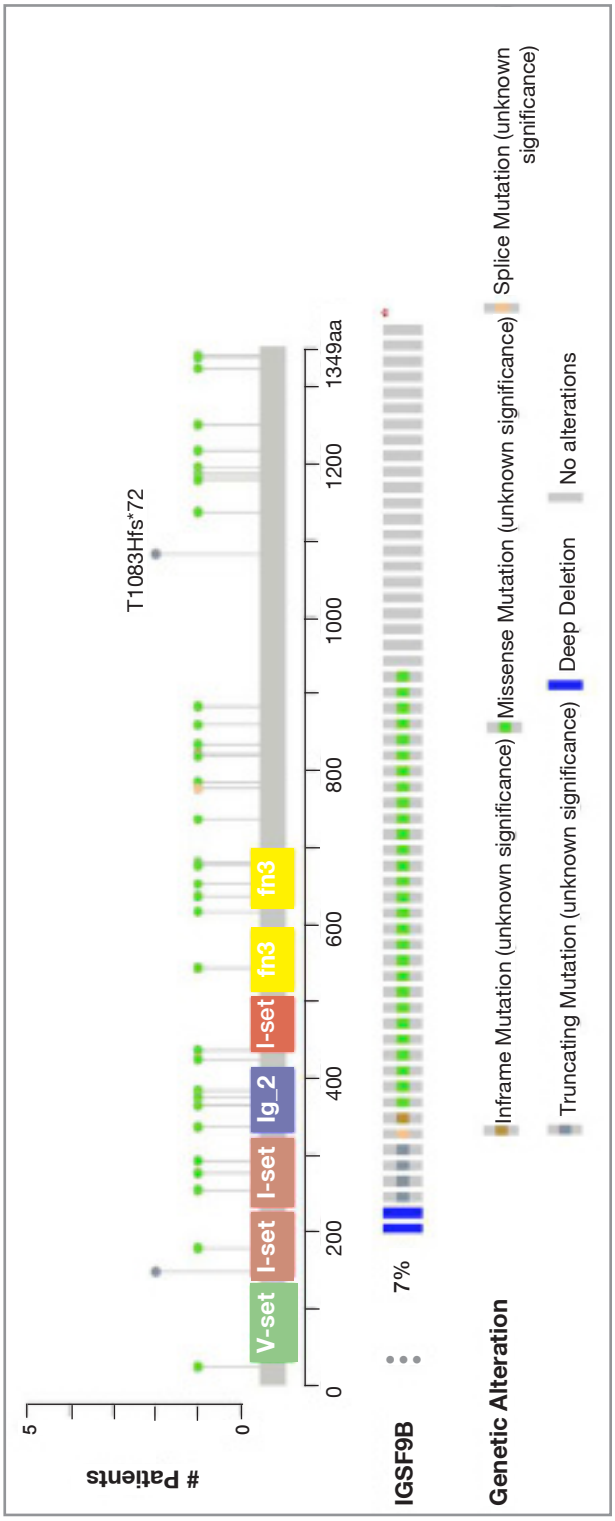

Figure 4. Alterations and mutations in the IGSF9B gene in the Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) dataset. Data obtained from https://www.cbioportal.org/ portal. *: "No alterations" continue until the 526th patient. V-set: Immunoglobulin V-set domain; I-set: Immunoglobulin I-set domain; Ig_2: Immunoglobulin domain; fn3: Fibronectin type III domain

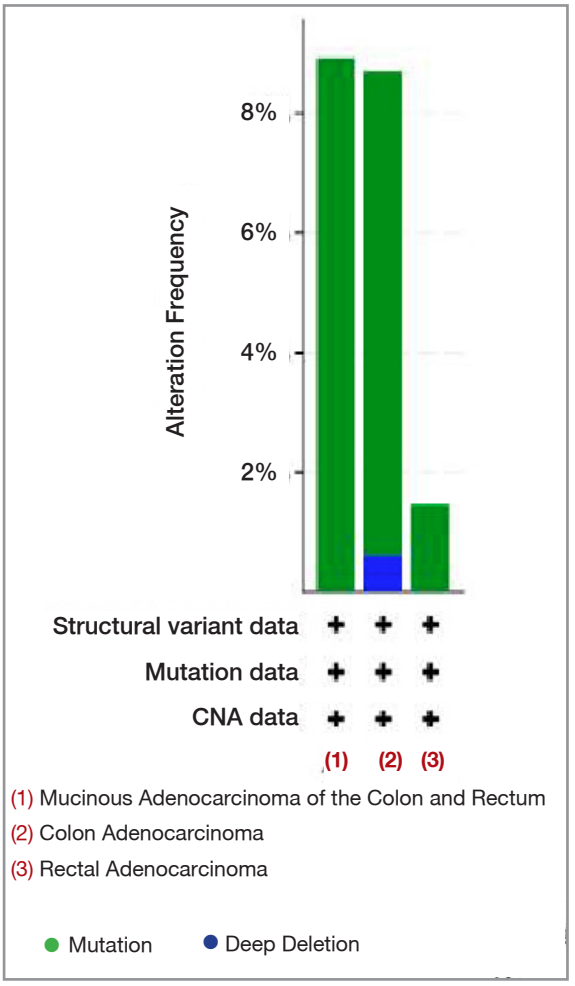

Figure 5. Distribution of alterations and mutations in the IGSF9B gene according to cancer types in the Colorectal Adenocarcinoma (TCGA, PanCancer Atlas) dataset. Data were obtained from the https://www.cbioportal.org/ portal

(328 - 413), 1 was on I-set: Immunoglobulin I-set domain (433 - 505), 1 was on fn3: Fibronectin type III domain (512 - 594) and 4 were on fn3: Fibronectin type III domain (622 - 698) (Figure 4).

Results of Correlation Analysis of IGSF9B Expression and Immune Infiltration

In the COAD cohort, the negative correlation between IGSF9B gene expression and tumor purity was not statistically significant. There was a significant weak positive correlation between IGSF9B gene expression and infiltration of CD4+ T cells, macrophages, neutrophils, and dendritic cells ($p= 7.01\times10^{-6}$, partial cor= 0.222; $p= 8.21\times10^{-5}$, partial cor.= 0.195; $p= 1.14\times10^{-6}$, partial cor. 0.24=; p=

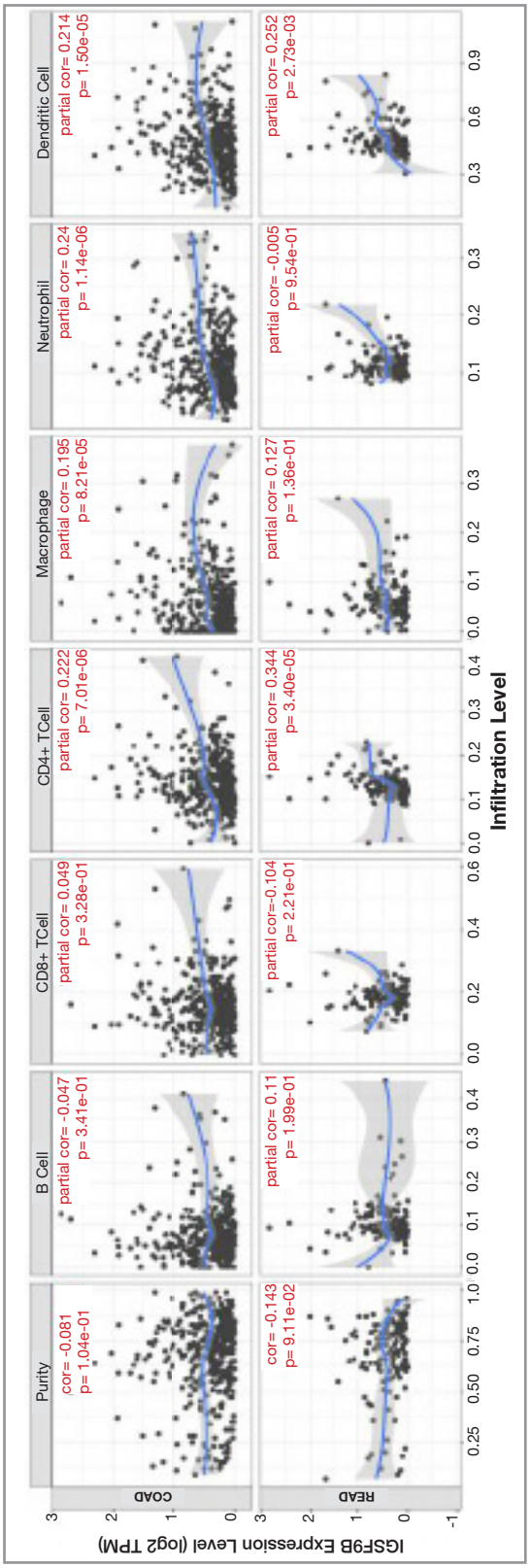

Figure 6. Relationship between IGSF9B expression and tumor infiltration levels of B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells. Web tool https://cistrome.shinyapps.io/timer/ was used.

1.50×10^{-5}, partial cor= 0.214), respectively (Figure 6).

In the READ cohort, the negative correlation between IGSF9B gene expression and tumor purity was not statistically significant. There was a significant weak positive correlation between IGSF9B gene expression and CD4+ T cells and dendritic cells infiltration (p= 3.40×10^{-5}, partial cor= 0.344; p= 2.73×10^{-3}, partial cor= 0.252, respectively) (Figure 6).

Results of Correlation Analysis Between IGSF9B Expression and Immune Checkpoint Inhibitors Target Gene Expressions

In the COAD cohort; a significant weak positive correlation was detected between IGSF9B gene expression and PDCD1, CTLA4, CD274 gene expressions (cor= 0.191, p= 3.72×10^{-5}; cor= 0.228, p= 8.44×10^{-7}; cor= 0.214, p= 3.86×10^{-6}, respectively). In the READ cohort; a significant weak positive correlation was detected between IGSF9B gene expression and only PDCD1 gene expression (cor= 0.251, p= 1.09×10^{-3}) (Figure 7).

Status of IGSF9B Expressions in Tumor and Normal Samples

Antibody staining in the tissue is reported as not detected, low, medium, or high based on conventional immunohistochemistry. Some examples showing the detection status of IGSF9B protein in COAD, READ and normal colon tissue are shown in Figure 8.

DISCUSSION

To our knowledge, our study is the first to demonstrate the relationship between the IGSF9B gene and CRC, and we have shown that IGSF9B gene expression is lower in patients with CRC than in normal individuals, and that lower expression is associated with better RFS and OS in cancer cases. Apart from this, our study is important in terms of demonstrating the relationship between IGSF9B levels and tumor microenvironment and PD1-PD L1 levels.

Adhesion molecules play an important role in leukocyte-cancer interactions and may support phagocytosis and antigen presentation by dendritic cells

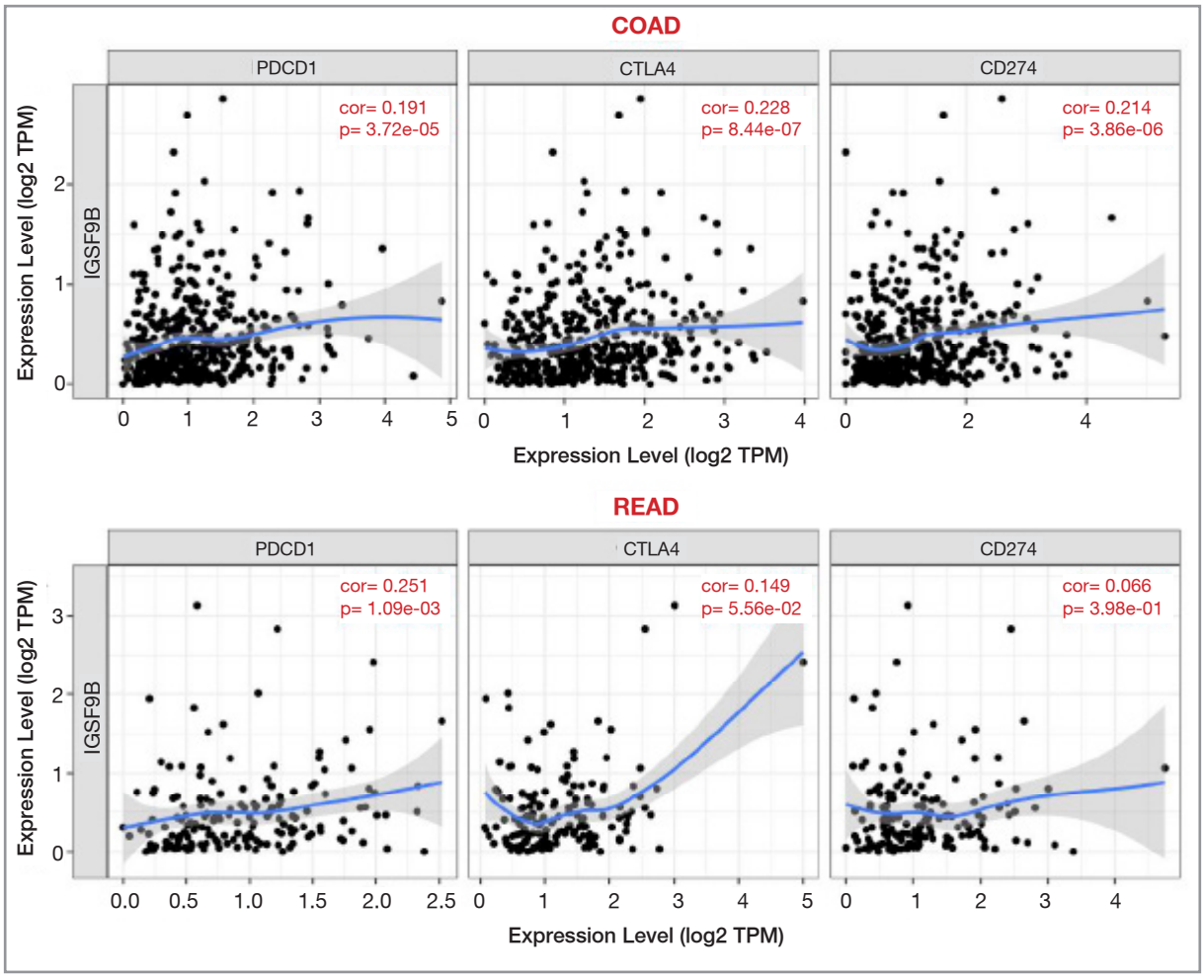

Figure 7. Relationship between IGSF9B expression and PDCD1, CTLA4, CD274 expression levels. https://cistrome.shinyapps.io/timer/ web tool was used.

interacting with cancer cells or anti-inflammatory effects. Integrin αE, which is also expressed by myeloid-derived suppressor cells and regulatory T cells, supports the pro- or anti-tumorigenic effects of immune cells, depending on the cellular context.[11] CAMs play important roles in the metastatic processes of CRC: downregulation of cadherins facilitates tumor cell detachment from the primary site, while expression of others, including IgSF, promotes progression, intravasation, and extravasation.[40]

IgSF CAMs are a group of transmembrane glycoproteins with extramembranous domains resembling immunoglobulins.[41] The best-known members of this superfamily are the major histocompatibility complex class I and II molecules and the T-cell receptor complex.[11] Others include PDGF receptors involved in immunological processes, neuronal CAMs responsible for cell integrity, and intercellular adhesion molecules. Downregulation or loss of expression of IgSF CAMs in lymphocytes leads to impaired recognition and elimination of neoplastic cells.[41] A number of IgSF members, such as platelet endothelial CAM-1 (CD31), Activated leucocyte CAM (CD166), and ICAM-1 (CD54), have been associated with metastatic progression in various malignancies, including colon cancer.[42]

IGSF9B, a member of IgSF CAMs and localized at inhibitory synapses in neuronal cultures, has been shown to be associated with schizophrenia and major depression.[12,43,44] After it was shown that many CAMs play a role in cancer pathophysiology, the effect of IGSF9B on cancer was also investigat-

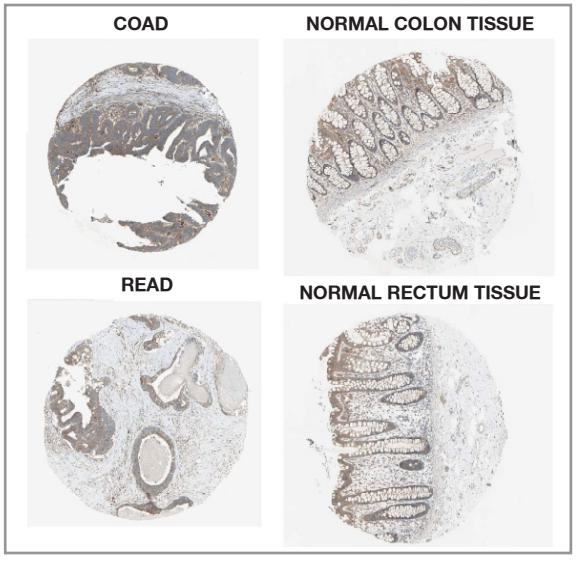

Figure 8: Antibody staining status of IGSF9B protein in one COAD and READ tissue and one normal colon and rectum tissue. Figures were obtained from The Human Protein Atlas database. URLs: IGSF9B COAD: https://www.proteinatlas.org/ENSG00000080854-IGSF9B/pathology/colorectal+cancer#img; IGSF9B normal colon tissue: https://www.proteinatlas.org/ENSG00000080854-IGSF9B/tissue/Colon#img; IGSF9B READ: https://www.proteinatlas.org/ENSG00000080854-IGSF9B/pathology/colorectal+cancer#img; IGSF9B normal Rectum: https://www.proteinatlas.org/ENSG00000080854-IGSF9B/tissue/Rectum#img. COAD: Colon adenocarcinoma ,READ: Rectum adenocarcinoma.

ed. Two different studies were conducted on this subject, both of which were bioinformatic studies involving breast cancer patients. In these studies, it was shown that an increase in IGSF9B expression was associated with shorter survival.[29,30] In our study, we also showed that IGSF9B expression was associated with shorter OS and RFS in the high cohort compared to the low cohort.

Immunocheckpoint inhibitors (ICIs show significant survival benefits in many types of cancer, and PD-1, PD-L1, and CTLA4 are target molecules for these treatments.[45,46] In our study, we showed that there is a positive correlation between IGSF9B expression and these markers. Further studies examining the effectiveness of CAMs and ICIs may be promising in the future, such as the interaction of drugs targeting these molecules with immune checkpoint inhibitors and, if necessary, combined use.

Classically, intense promoter DNA methylation is associated with suppression of transcription.[47] The lower gene expression in tumor samples with higher methylation in the COAD cohort can be explained by gene silencing due to high methylation, which fits the classical model. The fact that the control group consisted of a small number of samples (n= 7) may have been effective in the higher gene expression in normal samples with higher methylation in the READ cohort, thus making it difficult to make a sound interpretation in terms of methylation levels in the READ cohort. However, these results still suggest that epigenetic mechanisms may be effective in IGSF9B gene expression in CRC patients. In our study, we observed that frameshift mutations can lead to the formation of truncated proteins, specifically affecting the I-set domain (140-225) of the IGSF9B protein. These mutations include one Frameshift insertion (resulting in amino acid change Q147Pfs10) and one Frameshift deletion (resulting in amino acid change Q147Sfs13) within this domain. Additionally, two Frameshift insertions (resulting in amino acid change T1083Hfs*72) outside of this domain were also identified. These mutations can result in the formation of shortened and non-functional IGSF9B proteins. The IGSF9B proteins with altered functions that may occur as a result of this disruption may contribute to different stages of carcinogenesis and tumor progression. However, there is no literature data that can shed light on this possible mechanism.

Conclusions

Low expression of the IGSF9B gene may be a positive prognostic marker in CRC patients. Mutations in the IGSF9B gene and promoter region methylation changes may be effective in colorectal carcinogenesis. In addition, changes in the IGSF9B gene expression level may also affect processes related to the tumor microenvironment in colorectal carcinogenesis. However, experimental and clinical studies are needed to identify the downstream effectors of IGSF9B, a new molecule in oncology, and to elucidate the underlying mechanisms.

Data availability statement: The datasets obtained and analyzed during the study were collectively obtained from the following platforms: TGCA database (https://portal.gdc.cancer.gov/), the cBio Cancer Genomics Portal (http://www.cbioportal.org/), KM-Plotter database (https://kmplot.com/analysis/), UALCAN (https://ualcan.path.uab.edu/), GEPIA2 (http://gepia2.cancer-pku.cn/#index), GTEx (https://gtexportal.org/home/), TIMER (https://cistrome.shinyapps.io/timer/), The Human Protein Atlas database (https://www.proteinatlas.org/).

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