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RESEARCH ARTICLE

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OGG1 contributes to hepatocellular carcinoma by promoting cell cycle-related protein expression and enhancing DNA oxidative damage repair in tumor cells

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Abstract

Background: This study aimed to analyze the expression of 8-oxoguanine DNA glycosylase (OGG1) in patients with hepatocellular carcinoma (HCC) and its effect on prognosis by bioinformatics techniques and to determine its possible carcinogenic mechanism through data mining.

Methods: The difference in OGG1 expression between healthy people and HCC patients was searched and analyzed by TCGA and GEO databases, and the effect of OGG1 on prognosis was judged by survival analysis. Meanwhile, the possible molecular mechanism of OGG1 in the tumorigenesis and development of HCC was explored by GO analysis, KEGG analysis, immune infiltration analysis, protein–protein interaction network, promoter methylation analysis, and so forth. Quantitative polymerase chain reaction (qPCR) was used to examine the gene expression in 36 pairs of HCC tissues and adjacent tissues.

Results: The expression of OGG1 in HCC patients was higher than that in healthy people, and the overexpression of OGG1 might stimulate cell proliferation by increasing the activity of cell cycle-related proteins.

Conclusion: The alteration of OGG1 was significantly correlated with the tumorigenesis and development of HCC. OGG1 is expected to be a new biomarker for evaluating the prognosis of HCC and a new target for the treatment of HCC.

KEYWORDS
base excision repair, cell cycle-related proteins, hepatocellular carcinoma, OGG1

1 | INTRODUCTION

Hepatocellular carcinoma (HCC, LIHC) is a kind of primary liver cancer with high mortality.[1] Genetic and epigenetic changes, chronic hepatitis B, hepatitis C virus infection, aflatoxin exposure, smoking, obesity, and diabetes are the main risk factors for HCC.[2] In recent years, many studies focused on the molecular pathogenesis of HCC and found a series of genetic and epigenetic events that promote the tumorigenesis and development of HCC.[3]

Oxidative stress is usually increased in HCC, resulting in the increase of reactive oxygen species (ROS), then resulting in DNA damage, affecting the regulation of cell proliferation-related pathways, thus promoting the tumorigenesis and development of HCC.[4] The repair methods of DNA damage include mismatch repair, excision repair,

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homologous recombination repair, and so on.[5] Base excision repair (BER) is the main way to solve spontaneous, alkylation, and oxidative DNA damage.[6] It has been found that almost all cells contain different types of glycoside hydrolase, which can specifically remove the N-β-glycoside bond on damaged nucleotides and form depurination or depyrimidination sites on DNA.[7] 8-Hydroxy-2′-deoxyguanosine (8-oxo-dG) is an oxidizing adduct produced by singlet oxygen and reactive oxygen radicals like hydroxyl radical, which attack the eighth carbon atom of guanine. 8-oxoguanine DNA glycosylase (OGG1) is an important protein involved in BER, which widely exists in various tissues and is one of the most important proteases to repair 8-oxo-dG on DNA.[8] 8-oxo-dG is a kind of highly mutagenic injury, which leads to G : C to T : A mutation; thus, it plays an important role in tumorigenesis.[9] In addition, the 3p25-26 region of human chromosome in which the OGG1 gene is located is often lost in tumors, and its dysfunction may increase the susceptibility to various tumors including HCC.[10] For example, the research of Lee et al.[11] proved that E-cigarette smoke damages DNA and decreases the expression of OGG1, which may lead to an increase in the risk of tumorigenesis. Yousaf et al.'s study[12] showed that the dysregulation of OGG1 expression may promote the tumorigenesis and development of gastric carcinoma. Therefore, it is essential to make clear that how OGG1 contributes to HCC.

Thus, choosing OGG1 as the target and through a series of bioinformatics techniques, our study attempted to preliminarily explore the relationship between OGG1 expression and the tumorigenesis and development of HCC and find out the pathways that OGG1 mostly involved in. Subsequently, we focused on the cell cycle-related protein, which was fundamentally related to the tumorigenesis or development of HCC, and the qPCR tests were carried out to validate the correlation between OGG1 and the cell cycle. In general, our study may provide a new direction for the study of prognosis and molecular mechanism of HCC.

2 | MATERIALS AND METHODS

2.1 | Cell histochemical staining

To determine the expression sites and levels of OGG1, we used histochemical staining to analyze the 2 normal liver tissues and 3 liver tissues with HCC. Clinical information and pictures were all derived from the Human Protein Atlas (HPA) database (http://www.proteinatlas.org/), including specimen information and OGG1 protein localization.[13]

2.2 | Database analysis

We utilized the TCGA (http://cancergenome.nih.gov/) and GEO (http://www.ncbi.nlm.nih.gov/geo) databases to obtain data on OGG1 expression and clinical information of patients.[14] HCC patients and healthy people were divided into various groups according to sex, age, race, clinical stages, grades, histologic types, lymph node metastasis, and TP53 mutation. Statistical analysis was carried out to draw a column chart and survival curve. The staging of HCC was based on the eighth edition of the Joint Committee on Cancer (AJCC), and the grading was based on the Edmondson-Steiner grade.

2.3 | Promoter methylation analysis

Based on the Illumina 450 K microchip methylation data of TCGA database, MEXPRESS (https://mexpress.be/), an online tool, was used to screen the methylation level, methylation site, and CpG island location of the OGG1 gene in healthy people and HCC patients with different stages, grades, and TP53 mutation statuses.

2.4 | Protein–protein interaction network

The interaction between upstream and downstream proteins of OGG1 was searched by the STRING database (https://string-db.org/). Detailed information on each protein was analyzed and compared, and a network diagram of protein interactions was drawn by Cytoscape software.[15]

2.5 | GO analysis and KEGG analysis

Through DAVID (https://david.ncifcrf.gov/) and KOBAS (http://kobas.cbi.pku.edu.cn/anno_iden.php), we analyzed GO-CC (cellular component), GO-MF (molecular function), GO-BP (biological process), KEGG Pathway, and KEGG Reaction to clarify the function of OGG1 and the life activities it involved in.

2.6 | Immune infiltrates analysis

We used the TIMER database (https://cistrome.shinyapps.io/timer/) to analyze the correlation between OGG1 expression and the infiltration of certain immune cells, including B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells, in patients with HCC.[16] The variation in OGG1 gene copy number and the effect of immune cell infiltration on prognosis were also shown.

2.7 | RNA isolation and quantitative reverse transcription polymerase chain reaction analysis

Total RNA was extracted from liver tissues using the Total RNA Isolation Kit (Foregene, CN). The real-time PCR assay was performed using EvaGreen Express 2× qPCR MasterMix (ABM, CAN). Gene expression levels were determined using the comparative threshold cycle ($2^{-\Delta\Delta C_T}$) method with β-Actin as an endogenous control. Primers used for qPCR are shown in Table S1.

2.8 | Statistical analysis

Statistical analysis was carried out by SPSS 25.0 software. Continuous variables were compared using the Mann–Whitney *U* test. Categorical variables were compared using χ^2 test. Kaplan–Meier curves were used to compare the survival time differences, and differences between the curves were evaluated using the log-rank test. Correlations were assessed using the Pearson correlation coefficient. All statistical tests were two-sided, and the statistical significance was set at 0.05.

3 | RESULTS

3.1 | Increased expression of OGG1 in HCC

Through cell histochemical staining, we found that the main expression site of OGG1 in the cell was the nucleus (Figure 1A), and it was expressed in both the liver tissues of healthy people (Figure 1B,C) and HCC patients (Figure 1D–F).

The expression level of OGG1 in HCC patients was higher (Figure 1G). There was no significant difference in the expression level of OGG1 based on nodal metastasis status (Figure 1N), histologic type (Figure 1O), age (Figure 1J), sex (Figure 1K), or race (Figure 1L) of HCC patients. However, there were significant differences in the expression level of OGG1 in HCC based on TP53 mutation status (Figure 1I), stage (between T4 and other stages) (Figure 1M), and grade (between grade I and II and grade III and IV) (Figure 1H). In general, the expression level of OGG1 increased with TP53 mutation and worse stage and grade in HCC.

3.2 | High expression level of OGG1 indicates poor prognosis in patients with HCC

The survival rate of 182 HCC patients with relatively high and low expression of OGG1 was analyzed. The results showed that the disease-free survival rate (DFS) (Figure 2A) and overall survival rate (OS) (Figure 2B) in the high expression group were lower than those in the low expression group within 5 years.

3.3 | Decrease in OGG1 promoter methylation level in patients with HCC

Promoter methylation analysis of OGG1 based on TCGA data revealed the different methylation sites and levels of OGG1 (Figure 3A). The results included clinical information grouping, copy number change of OGG1 gene, and information of methylated sites. Statistical analysis showed that the level of OGG1 gene methylation in patients with HCC was decreased (Figure 3B). There were significant differences in the promoter methylation level based on TP53 mutation (Figure 3C), stage (between healthy people and T1, T2, and T3) (Figure 3E) and grade (grades I, II, and IV) (Figure 3D). The OGG1 gene methylation level in HCC patients with TP53 mutations was lower, and the worse the grade and stage of HCC was, the lower the methylation level was.

3.4 | Protein–protein interaction network of OGG1 in patients with HCC

The protein–protein interaction (PPI) network of OGG1 showed a variety of proteins related to OGG1, including apurinic/apyrimidinic endodeoxyribonuclease 1 (APEX1); thymine DNA glycosylase (TDG); methyl-CpG-binding domain protein 4 (MBD4); MutY homolog (MUTYH); single-strand-selective monofunctional uracil-DNA glycosylase 1 (SMUG1); X-ray repair cross-complementing protein 1 (XRCC1); cyclin O (CCNO); Nth-like DNA glycosylase 1 (NTHL1); polymerase (DNA directed); RNA terminal phosphate cyclase-like 1 (RCL1); and laminin subunit beta 1 (LAMb1). The functions involved include BER, DNA N-glycosylase activity, DNA and deoxyribose phosphate catabolic process, cell cycle and DNA replication (Figure 4).

3.5 | GO analysis and KEGG analysis of OGG1 in HCC

The results of GO analysis (listing the top 20 only) showed the molecular functions (Figure 5A), cell components (Figure 5B), and biological processes (Figure 5C) related to OGG1. This result indicated that OGG1 was mainly expressed in the nucleus, had catalytic activity and nuclease activity, and was involved in cell proliferation. The results of the KEGG database (listing TOP20 of the reaction database and TOP9 of the pathway database) showed that OGG1 was closely related to biochemical reactions such as DNA replication, cell cycle, and base mismatch repair and was also related to homologous recombination and DNA strand elongation (Figure 5D,E).

3.6 | Analysis of the correlation between OGG1 and immune infiltration in patients with HCC

In addition, we also carried out immune infiltrate analysis. After statistical analysis of the results derived from the TIMER database, there was no significant difference between the expression of OGG1 and the degree of infiltration of B cells, CD4+ T cells, CD8+ T cells, macrophages, neutrophils, and dendritic cells ($p > 0.05$) (Figure 6A). The survival analysis showed that there was no significant difference between the infiltration of these immune cells and the prognosis of HCC ($p > 0.05$) (Figure 6B,C). The high expression level of OGG1 did not change the infiltration of immune cells in the tumor microenvironment.

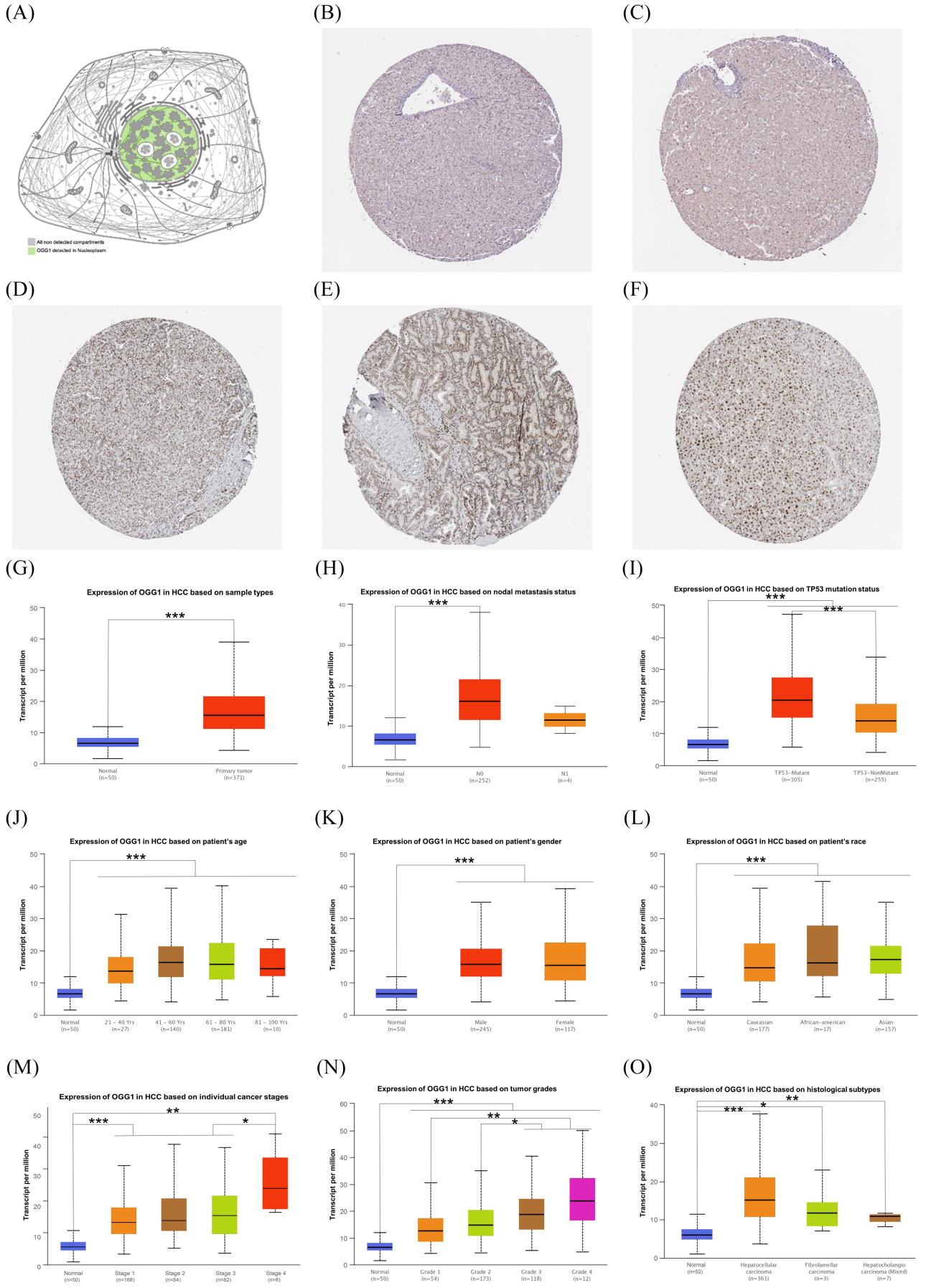

FIGURE 1 Expression of OGG1 in HCC, (A) expression of OGG1 in nucleoplasma, (B, C) OGG1 expression in healthy liver tissues, (D–F) OGG1 expression in liver tissues of HCC patients (G) expression of OGG1 in HCC based on sample type (H) nodal metastasis status (I) TP53 mutation status (J) age (K) gender (L) race (M) stage (N) grade (O) histological subtype

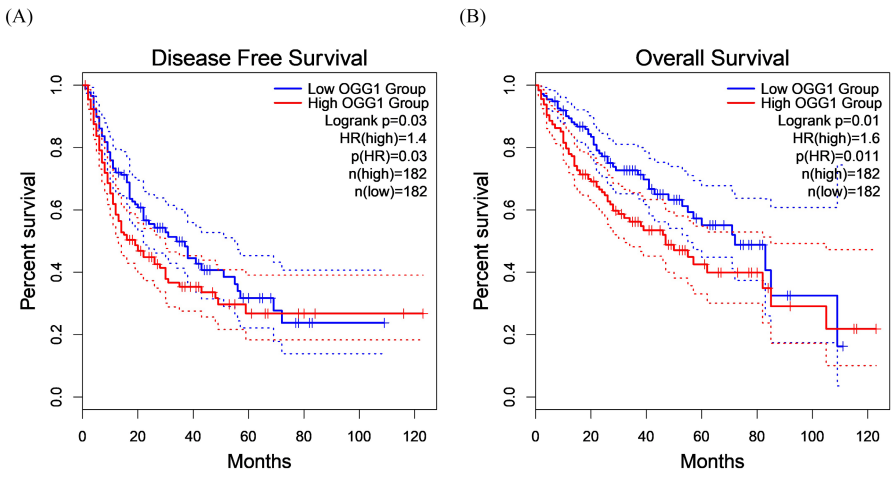

FIGURE 2 OGG1 expression is associated with survival outcome. (A) Disease-free survival: time from randomization to tumor recurrence, metastasis or death for any reason (B) Overall Survival: time from randomization to death for any reason

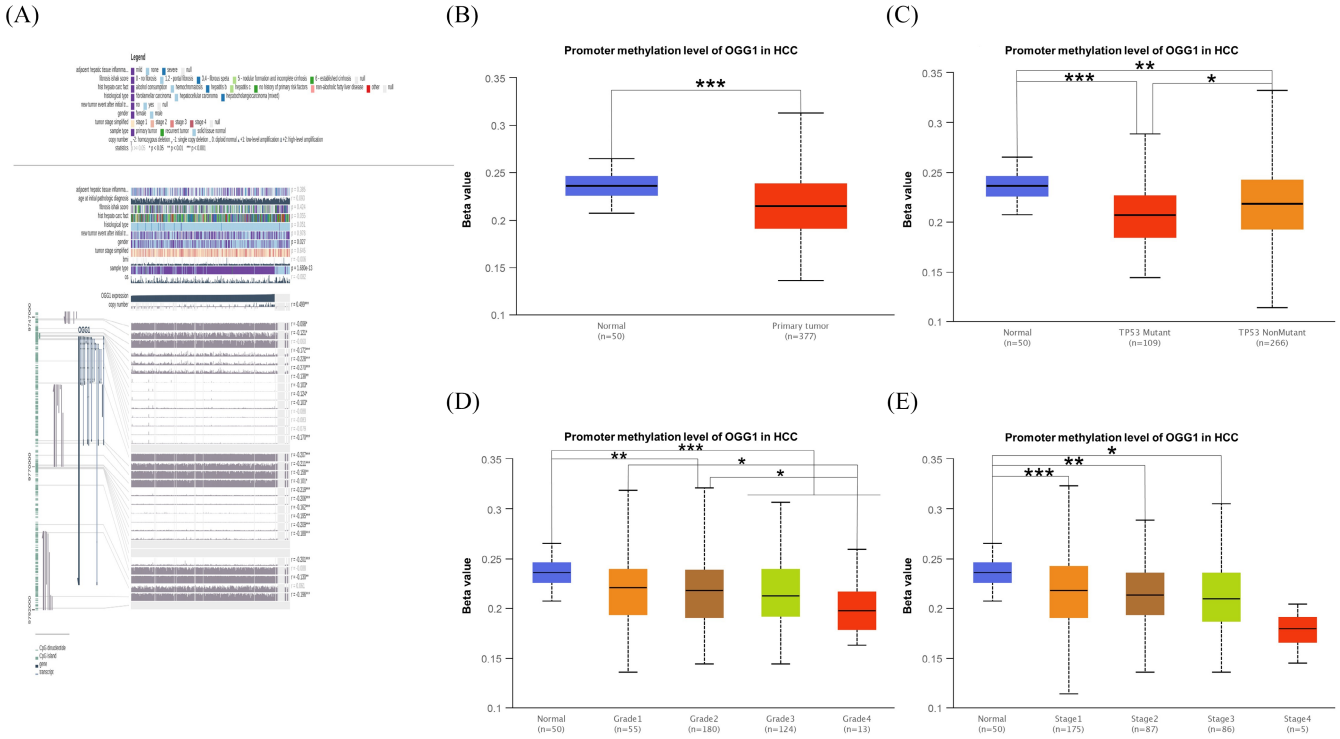

FIGURE 3 Promoter methylation analysis of OGG1 (A) Thermo-map of different methylated sites of OGG1 gene OGG1 promoter methylation level in HCC based on (B)sample type (C) TP53 mutation status (D) grade (E) stage (β value is used to measure the degree of methylation. Above 0.6: complete methylation 0.2 ~0.6: partial methylation <0.2: not methylated)

3.7 | Overexpression of OGG1 affects the expression of cell cycle-related proteins in HCC

We further verified the correlation between OGG1 and several cell cycle-related proteins. The results showed that the levels of six cell cycle-related proteins in HCC patients were increased and correlated with the expression level of OGG1 (Figure 7A). They were Cyclin A2 (CCNA2) ($p < 0.05$, $R = 0.18$) (Figure 7B), Cyclin B1 (CCNB1) ($p < 0.05$, $R = 0.39$) (Figure 7E), Cyclin-Dependent Kinase 1 (CDK1) ($p < 0.05$, $R = 0.43$) (Figure 7G), Checkpoint Kinase 1 (CHEK1) ($p < 0.05$, $R = 0.42$) (Figure 7D), Cell Division Cycle 25A (CDC25A) ($p < 0.05$, $R = 0.45$) (Figure 7C), and Cell Division Cycle 25C (CDC25C) ($p < 0.05$, $R = 0.4$) (Figure 7F).

3.8 | Identification of OGG1 and cell cycle-related proteins expression based on clinical samples

We used qPCR to examine OGG1 and cell cycle-related proteins expression in 36 pairs of HCC tissues and adjacent tissues (West China Hospital of Sichuan University, Chengdu, China, approval number: 2019203). All 36 cases of HCC clinical samples were

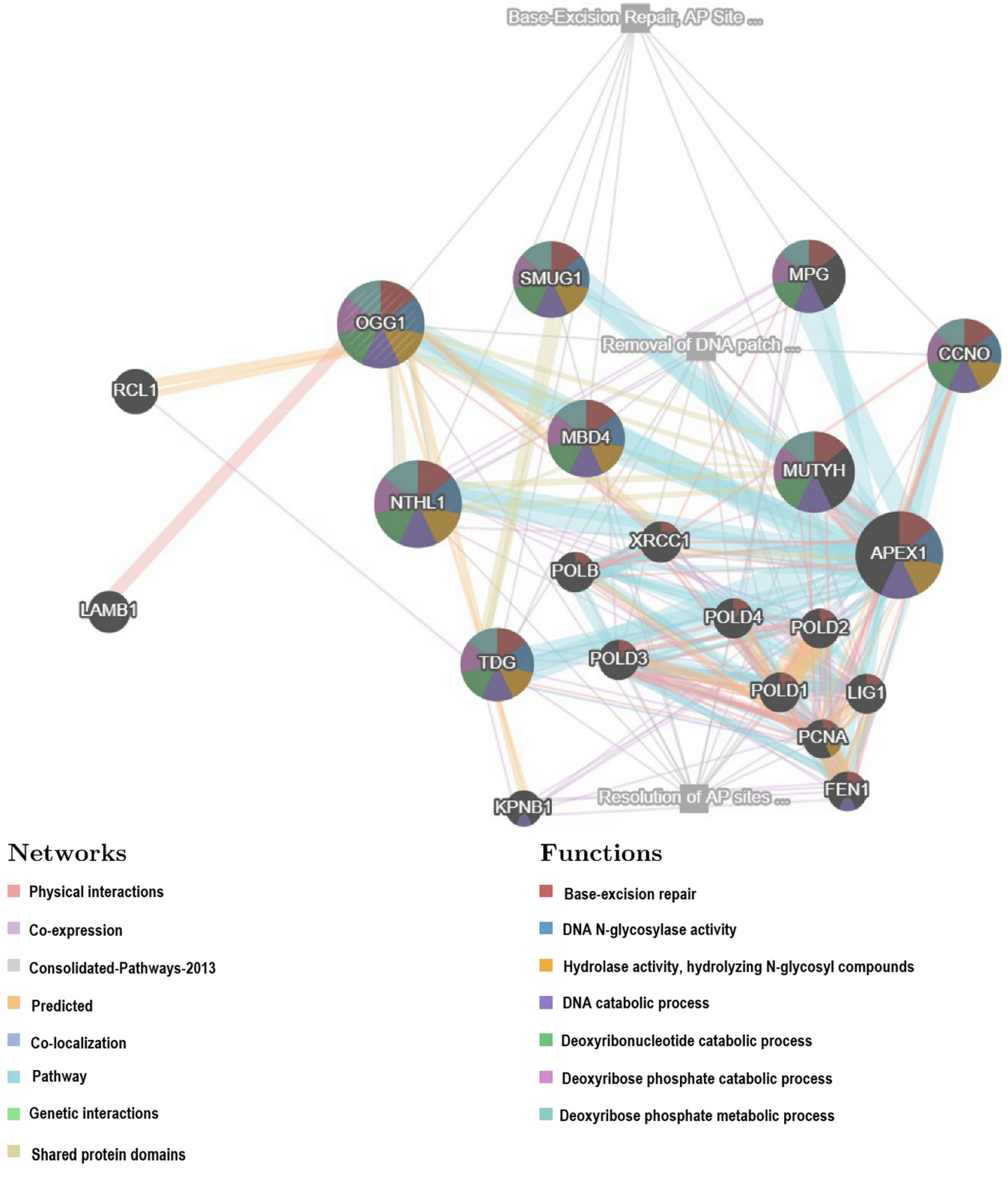

FIGURE 4 Protein–protein interaction (PPI) network of OGG1: Different color lines correspond to different interactions in the legend below, and the thicker the lines represent the stronger the interaction between proteins

definitely diagnosed by histopathology. The results confirmed that OGG1 and six cell cycle-related proteins (CCNA2, CCNB1, CDK1, CHEK1, CDC25A, and CDC25C) were increased in HCC patients (Figure 8A–G) and correlated with the expression level of OGG1 (Figure 8H–M). All results were statistically significant ($p < 0.05$).

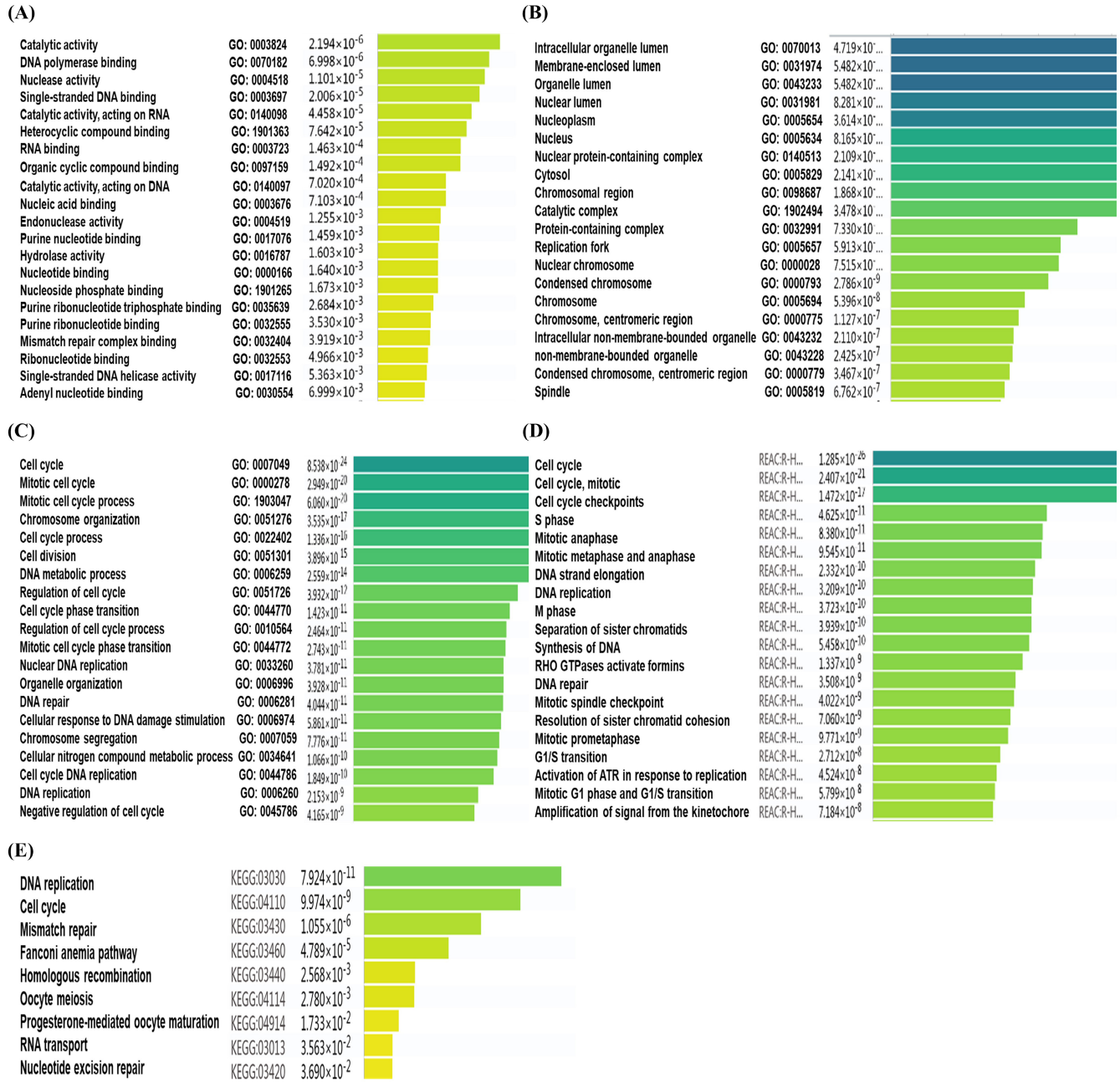

FIGURE 5 Results of GO analysis and KEGG analysis of OGG1 (A) GO-MF (molecular function): OGG1 gene products (B) GO-BP (biological process): biological processes and pathways in which OGG1 gene products participate (C) GO-CC (cellular component): localization of OGG1 gene products at subcellular level (D) KEGG Reaction: enzymatic reactions of OGG1 (E) KEGG Pathway: signal pathways of OGG1

4 | DISCUSSION

In HCC, chromosome instability and TP53 mutation occurred easily, leading to the activation of cancer pathway, the enhancement of oxidative stress, and the increase in oxidative modification.[17] As an important protein in DNA oxidative damage repair system, the expression level of OGG1 in HCC patients should be higher than that in healthy people.[18] Promoter methylation usually inhibited the endonuclease activity of OGG1, which meant that the lower the methylated level was, the stronger the function of OGG1 would be.[19] A study indicated that the OGG1 methylated defects and oxidative stress caused more DNA damage and increased mitochondrial Cytochrome C release in vitro.[20] In addition, the increase in OGG 1 methylation could keep the cell in G0/G1 phase and inhibit the cell proliferation.[21] In other words, the low level of OGG1 methylation and the high expression level of OGG1 in HCC proved that the body was in a state of oxidative damage and active cell proliferation. The interaction between upstream and downstream proteins of OGG1 also showed the potential correlation between its function and tumorigenesis. For example, APEX1 has the function of DNA

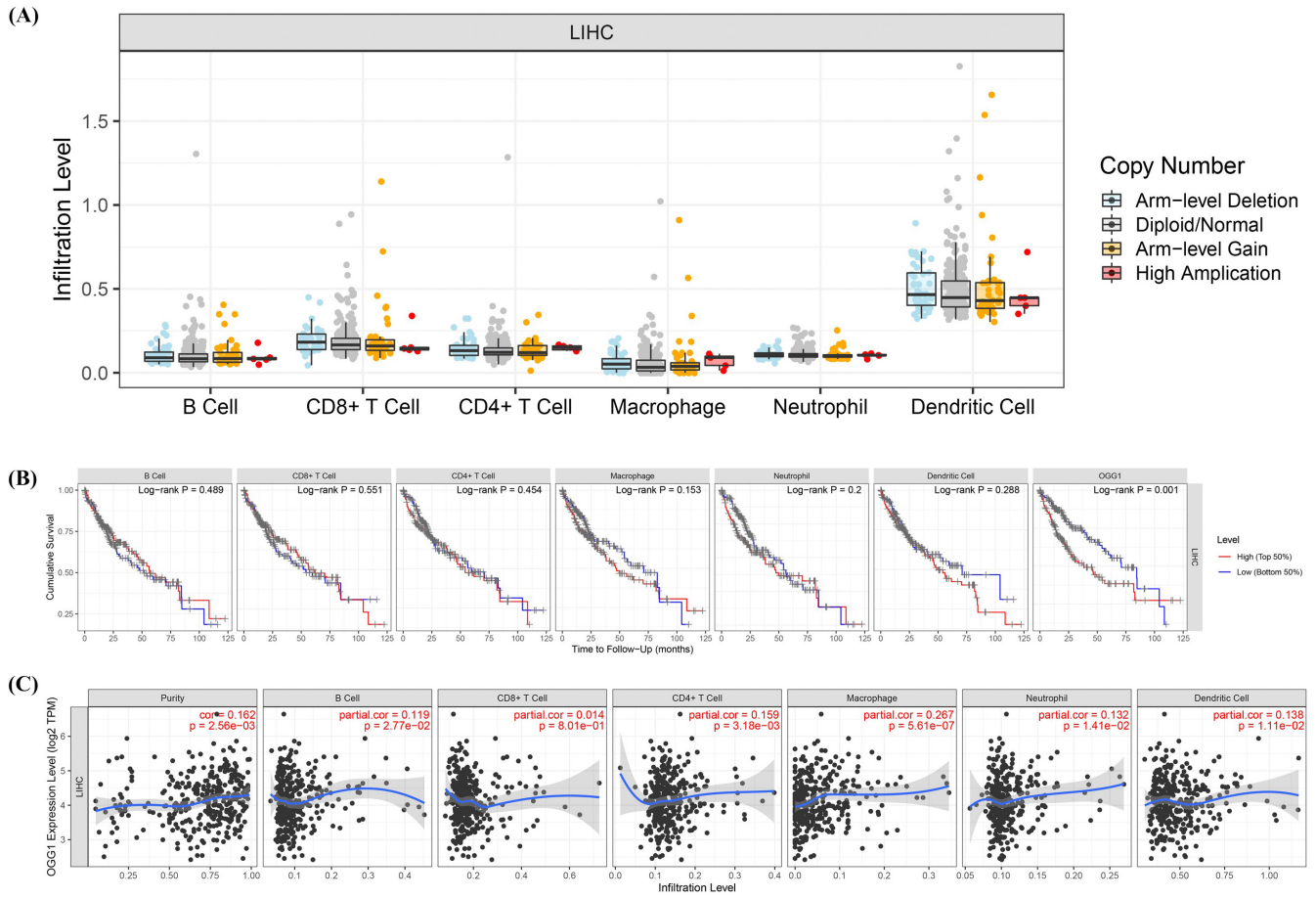

FIGURE 6 Immune infiltrates analysis of OGG1 expression in patients with HCC (A) the correlation between the copy number of OGG1 gene and the level of immune infiltration (B) the correlation between different OGG1 expression levels and immune infiltration (C) the survival analysis of immune infiltration

damage repair and redox, which can regulate a variety of transcription factors. Several studies had found that the expression of DNA was increased in a variety of malignant tumors, which was related to the clinical stage and prognosis of many kinds of malignant tumors.[22] TDG, as a co-activating factor of nuclear receptor, played an important role in maintaining cell epigenetic stability. It had also been confirmed that it was related to the tumorigenesis and development of HCC.[23] MBD4 was a member of MBD nucleoprotein family, which has glycosidase activity and can remove T and U bases mismatched with G, and was an important DNA damage repair protein.[24] At the same time, it also had the function of inhibiting transcription, regulating the level of methylation indirectly and regulating the process of apoptosis.[25] XRCC1 acted as a scaffold protein in BER, which could interact with several DNA repair-related proteins and recruited to DNA damage sites, and finally completed the repair of DNA.[26] These proteins, together with OGG1, were directly or indirectly involved in the repair of DNA damage and played an important role in maintaining the natural cell proliferation and the stability of DNA replication and transcriptional activity, which had the same potential as OGG1 as a biomarker of HCC.[27]

However, whether the high expression level of OGG1 not only served as a prognostic marker of HCC, but also promoted the tumorigenesis and development of HCC, was also worthy of further study. Although many studies had shown that the normal expression level of OGG1 played an important role in maintaining the high fidelity of DNA replication and ensuring the stability of biological inheritance,[28] it could not be ruled out that OGG1 may directly repair the DNA oxidative damage of tumor cells in patients, protect, and inhibit the killing of tumor cells.[29] It had been proved that a BER-related protein, MTH1 (MutT Homology 1), could efficiently degrade the oxidized free nucleotides in the nucleotides pool, thus reducing the fatal damage to tumor cells caused by high level of ROS.[30] Another possible explanation for the high expression level of OGG1 in HCC was that although studies had shown that oxidative damage repair genes like OGG1 highly expressed in patients with lung cancer, gastric cancer, breast cancer, and other tumors,[31] its repair effect was not enough to completely cope with the high level of oxidative damage in tumor microenvironment, resulting in the phenomenon of "invalid expression." That is, the high expression level of OGG1 might not promote the tumorigenesis and development of HCC, nor effectively inhibit the proliferation of tumor cells and repair the oxidative damage of DNA in tumor patients. At the same time, it was not ruled out that when OGG1 and other BER-related genes were overexpressed

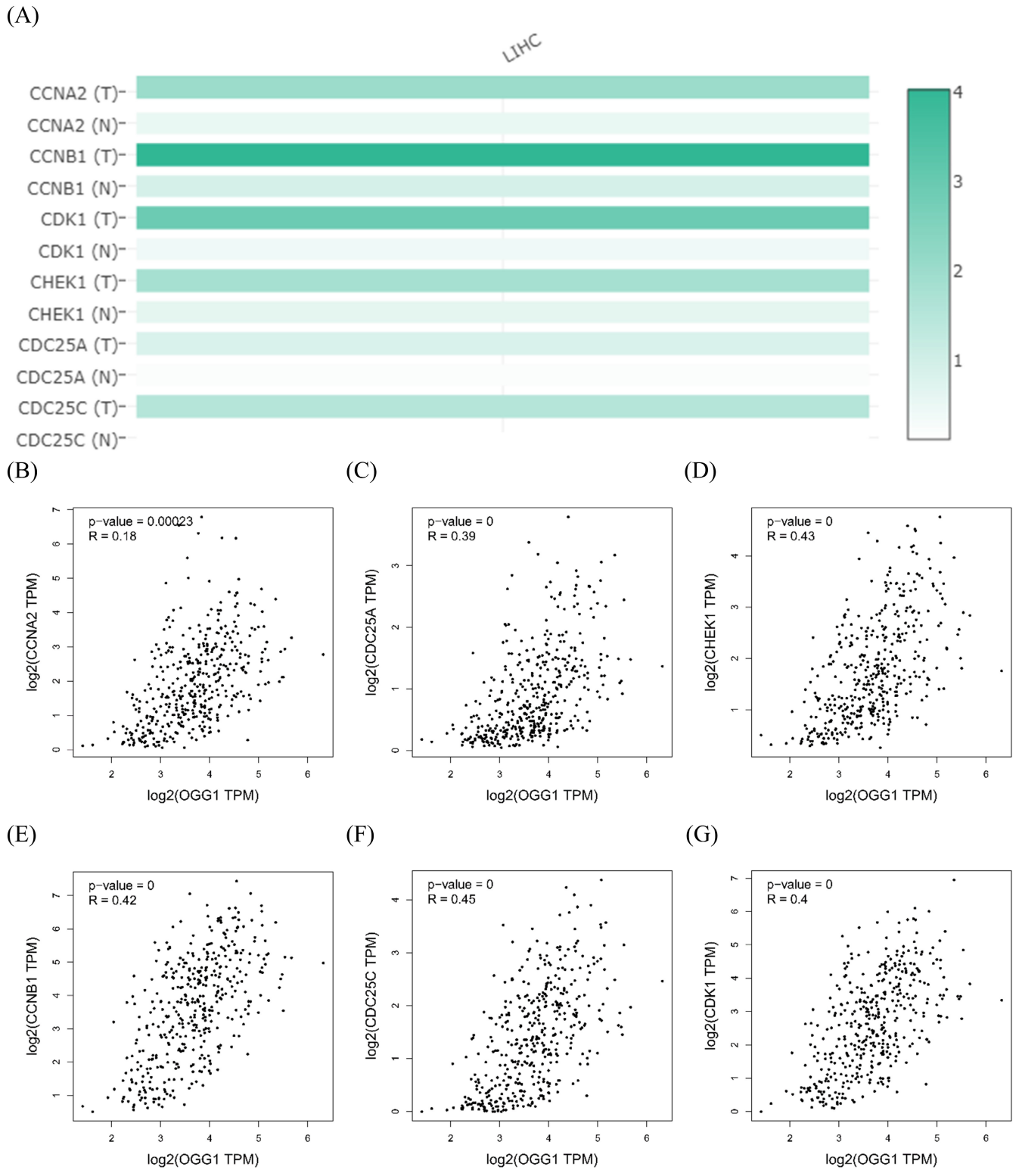

FIGURE 7 High expression level of six cell cycle-related proteins in HCC and their correlation with the expression level of OGG1 (A) the difference of cell cycle-related protein expression level between HCC patients and the healthy, and the correlation between OGG1 expression level and (B) CCNA2 (C) CDC25A (D) CHEK1 (E) CCNB1 (F) CDC25C (G) CDK1 expression levels (TPM, transcript per million)

in HCC, their excessive base excision might damage the DNA of some normal cells and increase the possibility of them becoming tumor cells.[32,33] In addition, since our analysis did not fully cover all the factors that may affect the expression of OGG1 and the tumorigenesis and development of HCC, it was not ruled out that patients with HCC might have abnormalities in DNA repair function (including but not limited to BER) due to risk factors like HBV infection.[34]

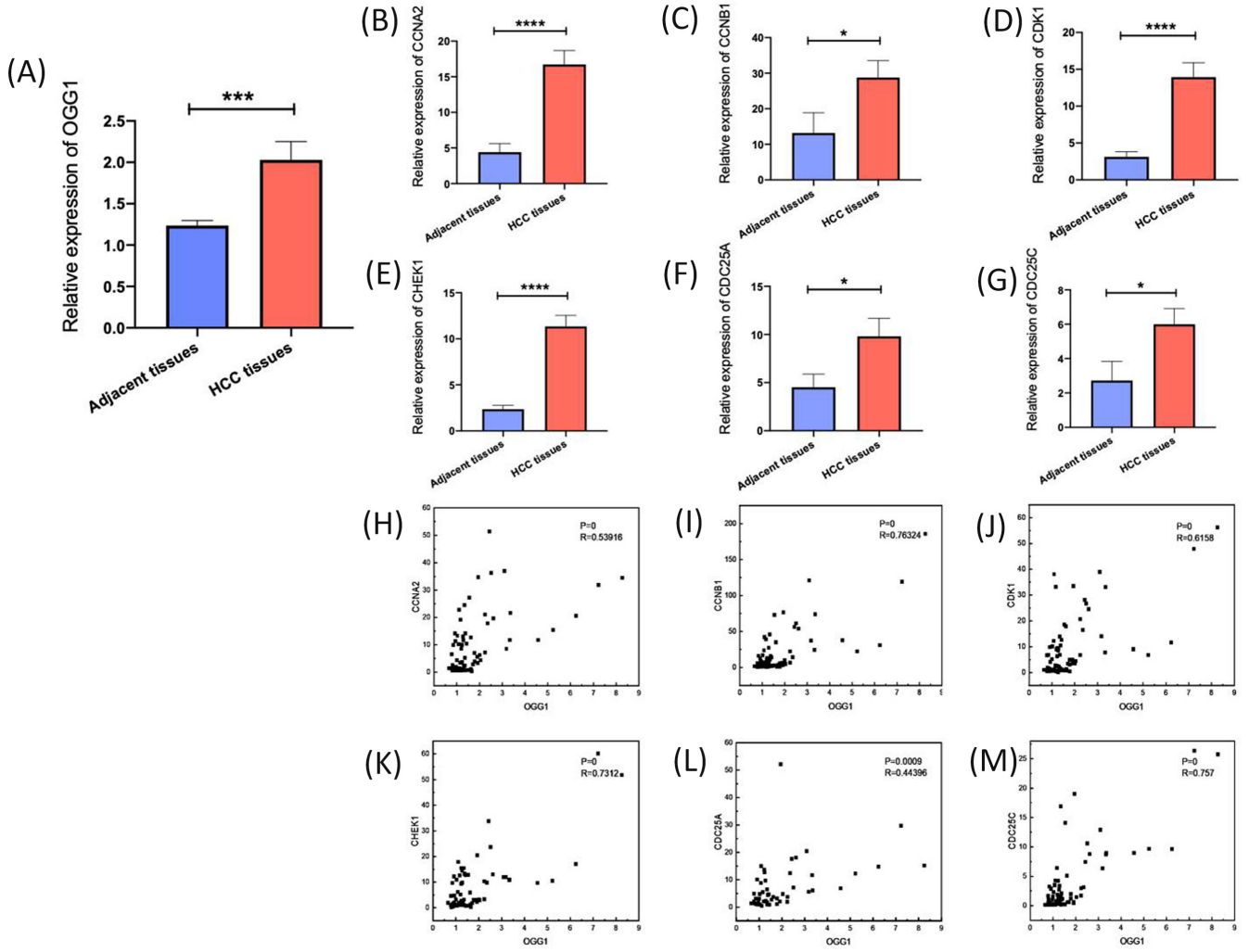

FIGURE 8 (A–G) Gene expression levels determined by qPCR in 36 pairs of HCC tissues and adjacent tissues (H–M) Correlation between OGG1 gene expression and six cell cycle-related proteins

Moreover, the results of qPCR confirmed that the high expression of OGG1 was related to the activation and overexpression of cyclin-dependent kinase, which protected the accuracy of DNA replication and promoted cell proliferation, thus promoting the occurrence and development of HCC.[35] Cell cycle was mainly regulated by Cyclin and CDK. Among the six proteins related to OGG1 expression level in HCC, CCNA2 was highly expressed in a variety of tumors, which played a key role in cell cycle control in G1/S phase and G2/M phase.[36] G2/M checkpoint was the control point that determined the division of cells and was also the last time for cells to repair DNA damage before mitosis.[37] It was reported that CCNA2 was upregulated in cancer tissues of HCC patients and could be used as a molecular marker for poor prognosis of HCC.[38] It was also reported that the upregulation of CCNB1 in primary liver cancer might be a potential biomarker to evaluate the prognosis of HCC.[39] In recent years, there was growing evidence suggesting that OGG1, in addition to DNA repair, played an epigenetic regulation role in transcription,[40] which could promote transcription of oncogene like c-Myc and inflammatory factors like CXCL1 and TNFα.[41,42]

In summary, OGG1 was highly expressed in HCC patients and was related to the grading, staging, and prognosis of HCC, which could be used as a potential biomarker for HCC. From the results of our mechanistic analysis, it could be inferred that there might be a mutually reinforcing relationship between the high expression level of OGG1 and the tumorigenesis and development of HCC. The high expression level of OGG1 might enhance the viability and promote the proliferation of tumor cells in two ways. One was to improve the oxidative damage repair ability of tumor cells, and the other was to activate cyclins and CDKs, thus promoting the tumorigenesis and development of HCC. With the development of HCC, oxidative stress increases, and the expression level of OGG1 might be further increased by its stimulation,[43] which formed a positive feedback loop.

ACKNOWLEDGMENTS

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CONFLICT OF INTEREST

The authors report no conflicts of interest.

DATA AVAILABILITY STATEMENT

Gene expression data analyzed in this study are available from The Cancer Genome Atlas (TCGA) (http://cancergenome.nih.gov/). The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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