Bioinformatics Analysis of Genes Upregulating Poor Prognosis In Colorectal Cancer And Gastric Cancer

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Research Article

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Bioinformatics analysis of genes upregulating poor prognosis in colorectal cancer and gastric cancer

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【**Abstract**】**Purpose**: To analyze the up-regulated genes of poor prognosis in colorectal cancer and gastric cancer by bioinformatics.**Methods:** We searched the gene expression profiles GSE156355 and GSE64916 in colorectal cancer and gastric cancer tissues in NCBI-GEO. With P value < 0.05 and log2>1 as the standard, Venn diagram software was used to identify the common DEGs in the two data sets. Kaplan Meier plotter was used to analyze the survival rate data of common differentially expressed genes, draw and select survival curves, and analyze their expression levels. **Results:** A total of 97 genes were detected to be up-regulated in the two gene expression profiles. There were 19 genes in the prognosis of gastric cancer and 15 genes in the prognosis of colorectal cancer that had significant differences in the survival rate. Among them, KCNQ1, TRIM29, GART, MSX1, SNAI1, SUV39H2, LOXL2 and KCTD14 significantly decreased the survival rate of gastric cancer and colorectal cancer. The expression of MSX1 was the highest in gastric cancer. The expression level of KCTD14 was the highest in colorectal cancer, and there was no significant difference in the expression levels of other genes. **Conclusion:** There are 19 and 15 genes with significantly different prognostic viability in gastric cancer and colorectal cancer, respectively. The survival rates of KCNQ1, TRIM29, GART, Msx1, SNAI1, SUV39H2, LOXL2 and KCTD14 were significantly decreased in gastric cancer and colorectal cancer. The expression of MSX1 was the highest in gastric cancer. The expression of KCTD14 was the highest in colorectal cancer.

【**Key words**】colorectal cancer gastric cancer Poor prognosis up-regulated gene bioinformatics

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Code availability: Not applicable.

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1 Materials and methods

1.1 Microarray data information

NCBI-GEO is seen as a microarray/gene map, and we got a gene microarray gene map, We search the NCBI - GEO (https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi) obtained in the tissue of colorectal cancer and stomach cancer gene expression profile GSE156355 and GSE64916. Gene expression profile GSE156355 was based on GPL21185 sequencing platform. Genome-wide microarray technology was used to compare the gene expression profiles of 6 colorectal cancer patients and 6 normal colorectal cancer tissues. Gene expression profile GSE64916 is based on the GPL13497 sequencing platform and uses the whole-genome and transcriptome analysis techniques to reveal the pathogenesis of peritoneal metastasis in advanced gastric cancer.

1.2 Screening of up-regulated differentially expressed genes (DEGs)

The screening of DEGS was identified by GEO2R online tool, and FDR (false discovery rate), which was corrected by P value, was the key index for differential gene screening. In the screening, P value < 0.05 and log2>1 were selected as the criteria (Fold Change represents the difference multiple) to screen out the up-regulated DEGS. Raw data in TXT format in the Venn software (online: http://bioinformatics.psb.ugent.be/webtools/Venn/) online check colorectal cancer and stomach cancer common DEGs two data set.

1.3 Gene ontology and pathway enrichment analysis

Gene ontology (GO) is a commonly used method to define genes and their RNA or protein products to identify unique biological characteristics of high-throughput transcriptome or genomic data. KEGG is a database covering genomes, diseases, biological pathways, drugs, and chemical materials. David was used to enrich BP, MF, CC and pathway of the screened up-regulated DEGs.

1.4 Survival analysis of core genes

Kaplan-Meier plotter [1]is a commonly used website tool, which is used to evaluate the effect of a large number of genes on survival based on EGA, TCGA database and GEO (Affymetrix microarray only), and to plot the survival curve of genes with common differential up-regulated expression in gastric cancer and colorectal cancer. Differential expression levels of genes that were significantly different in survival analysis between gastric cancer and colorectal cancer were analyzed.

2 Results

2.1 Identification of differentially up-regulated genes (DEGs) in colorectal cancer and gastric cancer

Through GEO2R online tool, the data of gene expression profiles GSE156355 and GSE64916 were extracted. With P value < 0.05 and log2>1 as the standard, the common DEGs in the two data sets were identified by Venn diagram software. A total of 2,494 and 805 DEGs were extracted from two datasets, GSE156355 and GSE64916, and the results showed that a total of 97 genes were detected to be up-regulated in the two gene expression profiles (Figure 1 and Table 1), which were the focus of this study.

Figure 1

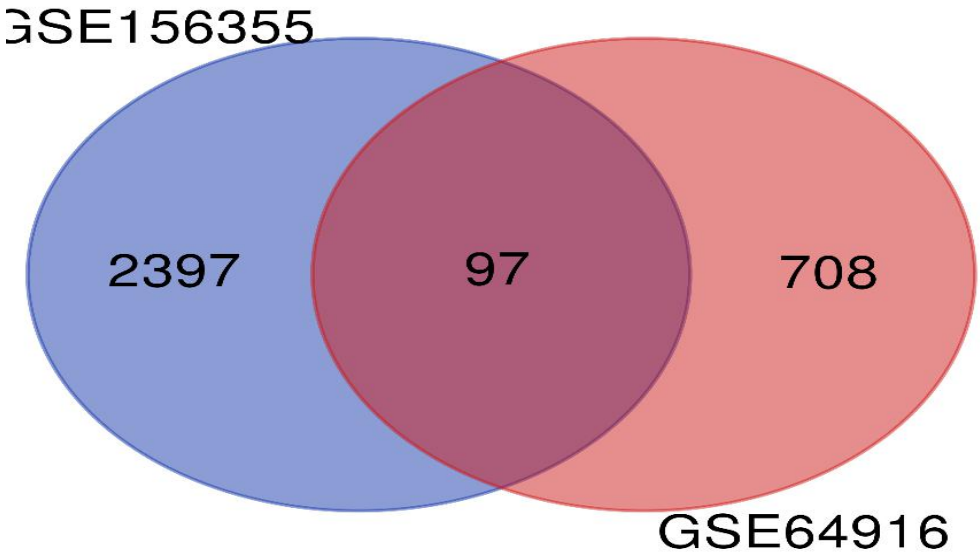


Fig1 Validates the common DEGs in two data sets (GSE156355 and GSE64916) using the Venn Diagrams software

Note: Different colors mean different data sets

Table 1 Total up-regulated differentially expressed genes (DEGs)

Table 1

Names of differentially up-regulated genes
KRT17，HILPDA，SERPINE2，SMIM13，REG3A，LOXL2，LAPTM4B，MTAP，HOXA9，FERMT1，TSPAN6，ERLIN2，UBD，TMPRSS3，POLR1C，THOC3，DNAH14，LZTFL1，PRMT5，IFITM3，C8orf33，FAM64A，SLC39A10，PRAME，PMEPA1，GNPDA1，CA9，TGM2，ZNRF3，NAV2，SP5，KCTD14，FADS3，IGF2BP3，KCNQ1，EPHX4
MMP11，MYEOV，TLCD1，LRRC8E，GPR56，KLHL35，CCND1，GART，MSX1，ZNF239，LRP11，ASIC1，KIAA0895，PACSIN3，PROSER2，SLC3A2，TRPM2，KRT80，PFAS，FTSJ2，LRRC34，TMEM139，SLC4A11，E2F6，ZFP69B，YARS，HNRNPA2B1，LPCAT2
ATR，SUV39H2，CCNO，CXADR，TRIM29，CDK8，NOP56，POU5F1，QPCT，TMEM245，ZP3，ARHGEF39，TNFRSF12A，IFITM2，STC1，FAM57A，SIX1，ZNF174，SUV39H1，AGMAT，C10orf35，SLMO1，SNAI1，S100A3，HTR1D，CELSR1，MED12

2.2 Gene ontology and pathway enrichment analysis of up-regulated differentially expressed genes in gastric cancer and colorectal cancer

The results of GO analysis showed that for biological processes (BP), the up-regulated DEGs were rich in negative regulation of RNA polymerase II promoter transcription, drug response, negative regulation of DNA templated transcription, cell cycle, etc. For molecular function (MF), up-regulated DEGs are rich in protein binding, protein dimerization activity, transcription cosuppressor activity, etc.

For cell components (CC) upregulated DEGs are rich in nucleoplasm, membrane components, cytoplasm, etc. (Table 2).

KEGG analysis results were shown in Table 3, indicating that up-regulated DEGs were enriched into the HSA00230 pathway of purine metabolism, including POLR1c, GART, and PFas genes.

Table 2 Gene ontology analysis of common up-regulated differentially expressed genes (DEGs) in colorectal cancer and gastric cancer

Table 2

分类 Category	Term	Count	p-Value	FDR
GOTERM_BP_DIRECT	GO:0000122~negative regulation of transcription from RNA polymerase II promoter	11	0.001065	0.667791
	GO:0035725~sodium ion transmembrane transport	4	0.003942	1
	GO:0034341~response to interferon-gamma	3	0.004836	1
	GO:0042493~response to drug	6	0.010374	1
	GO:0036123~histone H3-K9 dimethylation	2	0.012986	1
	GO:0007049~cell cycle	5	0.014749	1
	GO:0007605~sensory perception of sound	4	0.020199	1
	GO:0030178~negative regulation of Wnt signaling pathway	3	0.021487	1
	GO:0036124~histone H3-K9 trimethylation	2	0.021550	1
	GO:0060536~cartilage morphogenesis	2	0.0258058	1
	GO:0006189~'de novo' IMP biosynthetic process	2	0.0258058	1
	GO:0042754~negative regulation of circadian rhythm	2	0.0384612	1

GO:0035456~response to interferon-beta	2	0.0384612	1
GO:0035455~response to interferon-alpha	2	0.0426436	1
GO:0044070~regulation of anion transport	2	0.0426436	1
GO:0042118~endothelial cell activation	2	0.0426436	1
GO:0009952~anterior/posterior pattern specification	3	0.047390	1
GO:0060070~canonical Wnt signaling pathway	3	0.050615	1
GO:0043517~positive regulation of DNA damage response, signal transduction by p53 class mediator	2	0.0509545	1
GO:0051926~negative regulation of calcium ion transport	2	0.055083	1
GO:0009168~purine ribonucleoside monophosphate biosynthetic process	2	0.055083	1
GO:0003198~epithelial to mesenchymal transition involved in endocardial cushion formation	2	0.055083	1
GO:0009607~response to biotic stimulus	2	0.059194	1
GO:0060071~Wnt signaling pathway, planar cell polarity pathway	3	0.060741	1

	GO:0071456~cellular response to hypoxia	3	0.065447	1
	GO:0045892~negative regulation of transcription, DNA-templated	6	0.065880	1
	GO:0090280~positive regulation of calcium ion import	2	0.067363	1
	GO:0036342~post-anal tail morphogenesis	2	0.075462	1
	GO:0046597~negative regulation of viral entry into host cell	2	0.075462	1
	GO:0042474~middle ear morphogenesis	2	0.083492	1
	GO:0070588~calcium ion transmembrane transport	3	0.094641	1
GOTERM_MF_DIRECT	GO:0005272~sodium channel activity	3	0.002183	0.236464
	GO:0005515~protein binding	55	0.002341	0.236464
	GO:0046974~histone methyltransferase activity (H3-K9 specific)	2	0.023184	1
	GO:0000976~transcription regulatory region sequence-specific DNA binding	3	0.030189	1
	GO:0046983~protein dimerization activity	4	0.033305	1
	GO:0003714~transcription corepressor activity	4	0.069793	1
	GO:0035198~miRNA binding	2	0.072337	1
GOTERM_CC_DIRECT	GO:0005654~nucleoplasm	22	0.00764	0.502637

	GO:0016021~integral component of membrane	34	0.008742	0.502637
	GO:0005737~cytoplasm	33	0.018943	0.726145
	GO:0031012~extracellular matrix	5	0.041277	1
	GO:0016323~basolateral plasma membrane	4	0.04479	1
	GO:0005667~transcription factor complex	4	0.053115	1
	GO:0005730~nucleolus	8	0.081984	1
	GO:0005887~integral component of plasma membrane	11	0.090184	1

Table 3 KEGG Pathway analysis of differentially up-regulated genes in colorectal cancer and gastric cancer

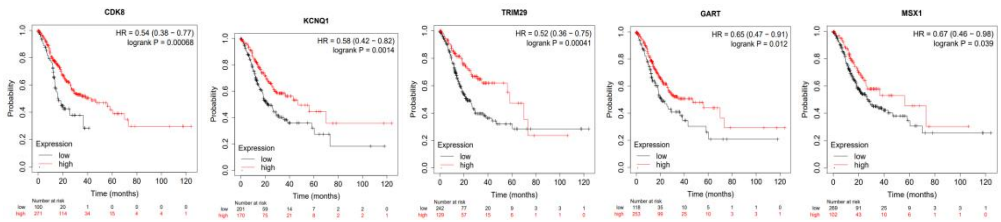
Table 3

Pathway ID	Name	Count	Genes	PValue
hsa00230	Purine metabolism	3	POLR1C, GART, PFAS	0.054942

2.2 Survival analysis of core genes

Kaplan Meier plotter (http://kmplot.com/analysis) for a total of differentially expressed genes of survival data statistics, drawing and survival curve ($P < 0.05$). The results showed that there were 19 genes with significant differences in survival rate in gastric cancer patients (Figure 2). There were 15 genes in prognostic colorectal cancer (Figure 3) that differed significantly in patient survival; Among them, KCNQ1, TRIM29, GART, MSX1, SNAI1, SUV39H2, LOXL2 and KCTD14 (Table 4) were significantly reduced in prognosis analysis of gastric cancer and colorectal cancer. The expression level analysis (Figure 4) showed that the expression level of Msx1 was the highest in gastric cancer. The expression of KCTD14 was the highest in colorectal cancer, and there was no significant difference in the expression of other genes.

Figure 2



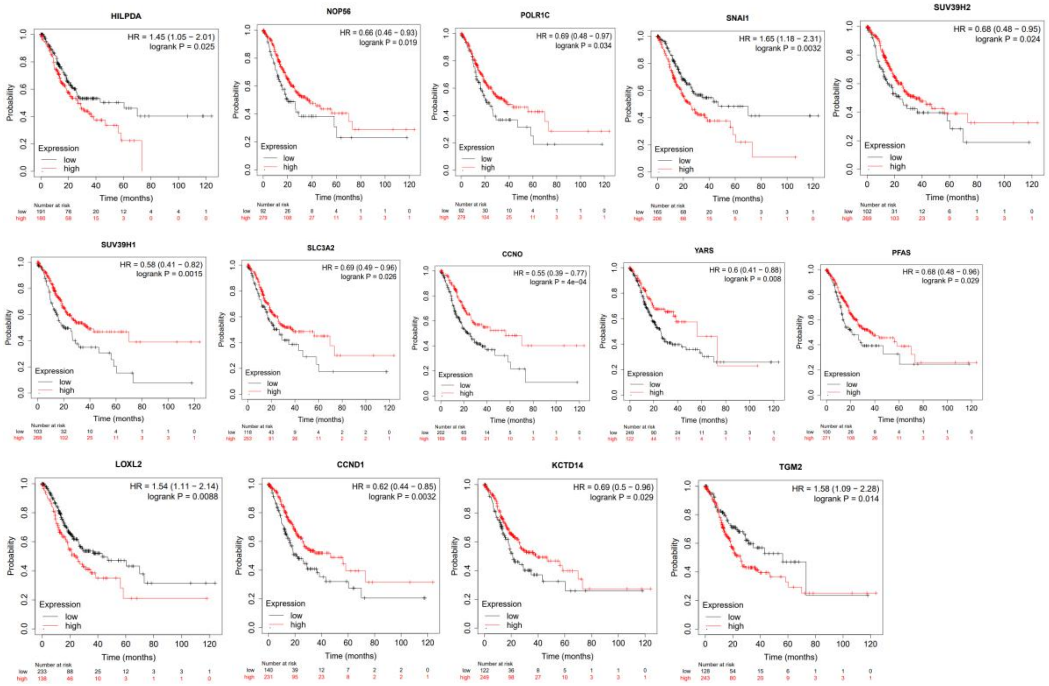
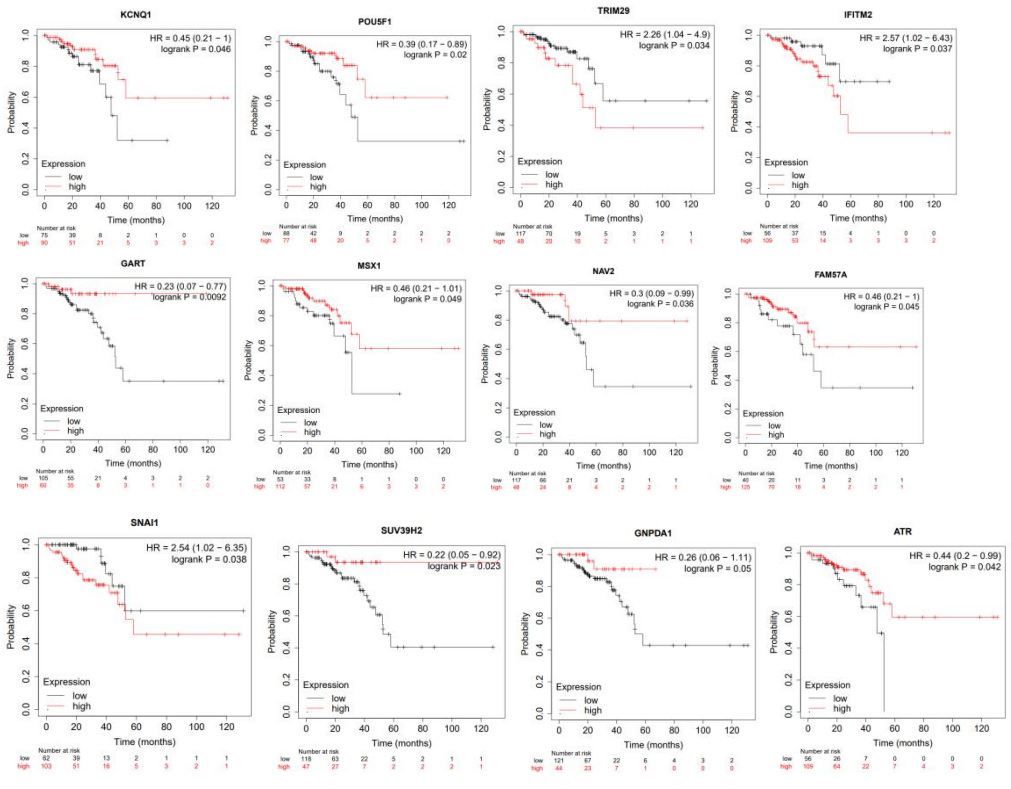


Fig. 2 Prognostic information of core genes in gastric cancer. The survival rate of 19 genes was significantly decreased (P<0.05) when Kaplan-Meier plotter was used to identify the prognosis of patients.

Figure 3



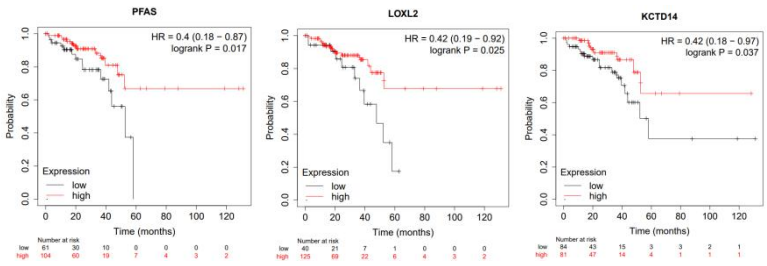


Fig. 3 Prognostic information of core genes in colorectal cancer. Using Kaplan-Meier plotter online tool to identify patients' prognosis information, the survival rate of 15 genes was significantly decreased (P<0.05).

Table 4 Genes differentially expressed in survival analysis of gastric cancer and colorectal cancer

Table 4

type	The name of the gene
Cancer of the stomach	CDK8 KCNQ1 TRIM29 GART MSX1 HILPDA NOP56 POLP1C SNAI1 SUV39H2 SUV39H1 SLC3A2 CCNO YARS PFAS LOXL2 CCND1 KCTD14 TGM2
Colorectal cancer	KCNQ1 POU5F1 TRIM29 IFITM2 GART MSX1 NAV2 FAM57A SNAI1 SUV39H2 GNPDA1 ATR PFAS LOXL2 KCTD14

Figure 4

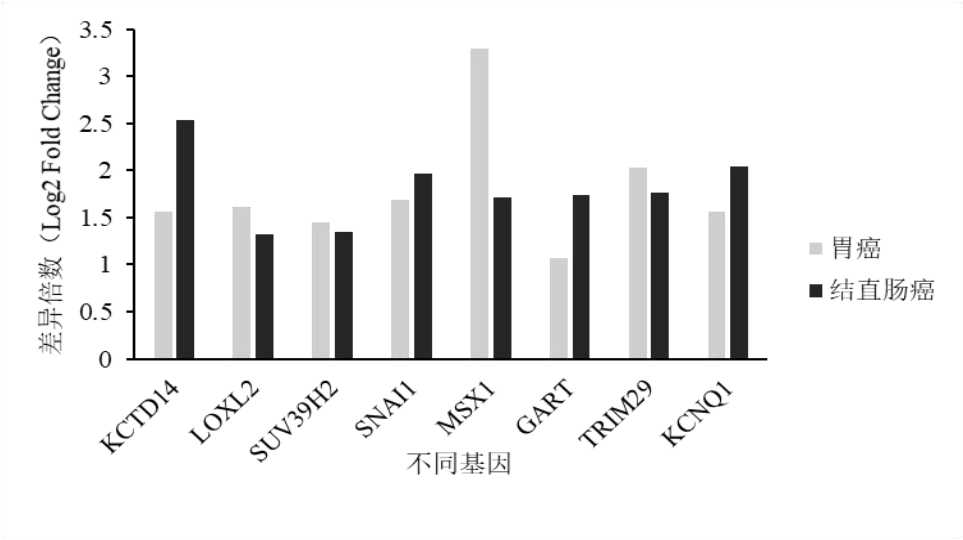


Fig. 4 Differential expression levels of genes with poor prognosis common to both cancers

3 Discuss

Gastric cancer and colorectal cancer are malignant gastrointestinal tumors with high morbidity and mortality in the world. The prognosis of patients with colorectal cancer and gastric cancer has a serious impact on the quality of life of patients. The occurrence of digestive tract tumors is closely

related to gene regulation, environmental factors and dietary habits. At present, it is believed at home and abroad that gene regulation is still the main factor of the disease, and the prognosis of gastric cancer and colorectal cancer is also closely related to many genes [2-4].

In order to identify the expression of more differential genes in digestive tract tumors, gene profiles GSE156355 and GSE64916 were screened in the NCBI-GEO microarray database. A total of 97 genes were detected to be up-regulated in the two gene expression profiles with P value < 0.05 and log2>1 as the standard. Kaplan Meier plotter was used to analyze the survival rate data of shared differentially expressed genes, and survival curves were drawn and selected (P<0.05). The results showed that there were 19 genes with significant difference in survival rate in patients with gastric cancer. In colorectal cancer, there were 15 genes with significant differences in patient survival; Among them, 8 genes, KCNQ1, TRIM29, GART, MSX1, SNAI1, SUV39H2, LOXL2 and KCTD14, were significantly reduced in prognosis and survival rate in gastric cancer and colorectal cancer. The expression level of MSX1 was the highest in gastric cancer. The expression of KCTD14 was the highest in colorectal cancer, and there was no significant difference in the expression of other genes.

Studies have found that gastric cancer is the second largest cause of cancer death in the world, and it is a common malignant tumor in China. How to achieve early diagnosis and early surgery is an important factor to determine the prognosis of patients. For patients in advanced stage, postoperative recurrence and drug resistance, the effect of radiotherapy and chemotherapy is poor and the toxic side effects are large, and effective treatment is lacking. Therefore, it is urgent to find specific molecular markers for early cancer diagnosis and effective treatment with low toxicity [5, 6]. Luo L[7]found that there is hypermethylation and silencing of the promoter CpG island of several tumor suppressor genes in gastric cancer, including the Wnt antagonist DKK3 and the newly discovered candidate gene Msx1 gene, which can be up-regulated after demmethylation, indicating that it is an ideal target for tumor treatment. As a newly emerged Msx1 gene, the expression difference of Msx1 in precancerous lesions and gastric cancer tissues can be further understood in large clinical samples, and whether it is an early tumor molecular marker can be studied. And further study its function as a tumor suppressor gene and its mechanism. Bioinformatics analysis in this study also confirmed this point, and MSX1 gene is closely related to the occurrence of gastric cancer, which can be used as an important indicator of detection and an effective target in the diagnosis and treatment of gastric cancer.

Studies have shown that the low expression of the homologous gene KCTD11 of KCTD14 is associated with poor prognosis. The overexpression of KCTD11 inhibates the proliferation and migration of lung cancer cells, and the results are reversed after knockout[8, 9] . Tong Rongliang[10, 11] also found low expression of KCTD11 in the tissues of patients with hepatocellular carcinoma. Heterozygosity loss is one of the causes of low expression of KCTD11, and low expression of KCTD11 suggests poor long-term prognosis. Natural killer cells (NK cells) are effector cells of the natural immune system, which play an important role in resisting pathogen invasion and anti-tumor, and the negative regulation of KCTD9 molecule plays an important role in the proliferation of NK cells[12-14] . Li Yu[15] , Zhou Xiaolong [16] and Liu Zhuoqing[17] demonstrated the relationship between KCTD14 gene and the migration and invasion of breast cancer cells, cell proliferation and its expression differences as well as its clinicopathological significance. In this study, it was found that the expression of KCTD14 was the highest in colorectal cancer. KCTD14 gene is closely related to the occurrence of colorectal cancer, and can be used as an important indicator for detection and an effective target for diagnosis and treatment of colorectal cancer.

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