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IDENTIFICATION OF NEW DIFFERENTIAL EXPRESSED GENES OF ESOPHAGEAL CANCER

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Abstract

Esophageal cancer (ESCA) is a type of gastrointestinal malignancy. It has one of the lowest survival rates among all types of cancer. Exploring ESCA related genes can help reveal the mechanism of ESCA occurrence and development and develop new diagnostic biomarkers and therapeutic targets. In the current study, three genes including ADCY3, CAB39L and TCOF1 were identified by bioinformatics analysis to show differential expression in ESCA and the adjacent normal tissues. Among the three genes, ADCY3 and TCOF1 were up-regulated, whereas CAB39L was down-regulated in the cancerous tissues. Survival analysis suggests that the expression levels of these genes have no impact on overall survival when analyzed individually. However, in combination analysis, patients with low expression of ADCY3 but high expression of TCOF1 show severe adverse outcomes with the lowest survival level. Therefore, the result suggests the combination of these genes could act as biomarkers for prognostic evaluation.

Keywords: *Esophageal cancer; ADCY3; CAB39L; TCOF1; differential expression*

1. Background

Esophageal cancer (ESCA) is a common gastrointestinal malignancy including *esophageal* squamous cell *carcinoma* (ESCC) and *esophageal* adenocarcinoma (EAC) (Watanabe, et al., 2020). ESCA affecting people from all over the world. There are many factors that will lead to ESCA. The known factors are people' gender (male are more likely to get ESCA than female), ages (older than 50 years old), ethnicity, past diseases (Gastro-esophageal Reflux Disease and obesity), and living habits (alcohol consumption, smoking, and diet) (Huang & Yu, 2018).

ESCA only has a 5-year survival rate of about 20% and can be ranged from 12 to 39% (Lewis & Lukovic, 2022). Currently, ESCA is primarily diagnosed during its advanced stages because of lack of early clinical symptoms and prognosis of ESCA for scientists to identified (Domper Arnal, et al., 2015). Therefore, the lack of prognosis and rising incidence of ESCA shows that detection and prediction methods for ESCA is vitally essential for

researchers to do, so as to improve the survival rate of ESCA patient (Huang & Yu, 2018).

Currently, scientists have already identified multiple genes in human body that are responsible for the cause and development of ESCA (Lewis & Lukovic, 2022). Studies have shown that genes that control the cell cycle are often overexpressed, such as CDKN2A, RB1, and NFE2L2 et al (somatic mutation in TP53) (Huang & Yu, 2018). Other factors leading to ESCA including epidermal growth factor receptor, receptor tyrosine kinase, epigenetic factors, and vascular endothelial growth factor signal pathway (Huang & Yu, 2018). There are still a large proportional of mutated genes and biological process in human body stay unknown for scientists. Identification of novel genes involved in ESCA occurrence and development will contribute to the development of new diagnostic biomarkers and therapeutic targets. Therefore, the current study aimed to find new genes which are not being previously published relating to ESCA, and three genes were successfully identified in the final.

2. Methods

2.1 Finding Differential Expressed Genes (DEGs)

The gene expression data of 23 patient cases of ESCA tissue and the paired adjacent normal tissues were obtained from Gene Expression Omnibus (GEO) database (https://www.ncbi.nlm.nih.gov/geo) with the accession number of GSE130078 (You et al., 2019). Differentially expressed genes (DEGs) were analyzed by the online tool GEO2R (Barrett, et al., 2013). Significantly up-regulated genes and down-regulated genes were selected to be DEGs with the cutoffs of |log2(foldchange)|>=1 & p value <= 0.05. The Cancer Genome Atlas (TCGA) esophageal carcinoma datasets were also used for the comparison between normal and cancerous gene expression of DEGs. The data of cancer and para-cancer expression of ESCA for genes were obtained from University of California Santa Cruz Xena (UCSC Xena) (Goldman, et al., 2020). Selected DEGs were obtained based on the intersection of GEO differentially expressed genes and TCGA esophageal carcinoma database meeting the result of statistical significance.

2.2 Functional Enrichment Analysis

A functional enrichment test was performed to DEGs by The Database for Annotation, Visualization, and Integrated Discovery (DAVID) Functional Annotation Bioinformatics Microarray Analysis (Sherman et al., 2022). DEGs associated with biological process (BP) of gene ontology (GO) and KEGG pathway categories having a p-value lower than 0.05 were selected.

2.3 Statistical analysis

Paired Student's t-tests were performed by GraphPad Prism v8.0 to compare the expressional difference between the paired cancerous and adjacent normal tissues of multiple individuals. Level of significance was set as $p < 0.05$.

2.4 Survival analysis

The UALCAN (University of ALabama at Birmingham Cancer) data analysis portal (https://ualcan.path.uab.edu/) was used for TCGA data analysis (Chandrashekar, et al., 2022). Genes in comparison that have a p-value lower than 0.05 are referred as having a statistically significance and genes in comparison that have a p-value lower than 0.01 are referred as having a highly statistically significance.

The effects of multiple gene combination of expression on patient survival were analyzed online using ToPP database (http://www.biostatistics.online/topp/index.php). Median was used to group gene expressions.

3. Results

3.1 Result of Differential Expressed Genes

The aim of the current study is to discover new genes associated with the development of ESCA. Firstly, I identified the interested ESCA datasets from the GEO database and used the online tool GEO2R to identify differentially expressed genes (DEGs) between the cancerous and the adjacent normal tissues. Totally, 182 DEGs, including 112 up-regulated and 70 down-regulated DEGs were successfully identified. Because the DEGs were derived only from one dataset, in order to increase the reliability, these genes were further checked using another dataset from the TCGA project. Therefore, the intersected up- and down-regulated genes were identified.

Totally, 78 genes including 70 up-regulated and 8 down-regulated genes, which had a statistically significance in both datasets, were successfully identified (Table 1).

Table 1. – *Differentially expressed genes of ESCA supported by both GEO and TCGA datasets* *

Type	Gene	Log2 (fold-change)	P value (GEO)	P value (TCGA)	Type	Gene	Log2 (fold-change)	P value (GEO)	P value (TCGA)
Up	INHBA	3.12	7.06E-46	7.88E-05	Up	DNMT3B	1.75	1.11E-25	1.62E-12
Up	SERPINE1	2.51	4.16E-43	2.21E-07	Up	HOMER3	5.111	1.18e-25	2.00E-04
Up	STC2	2.485	1.27E-41	5.60E-11	Up	ADAM12	3.082	1.62E-25	2.11E-15
Up	MAPK12	2.711	2.83E-40	2.70E-09	Up	CHN1	2.715	2.06E-25	3.40E-02
Up	SNX10	3.41	2.26E-38	1.62E-12	Up	PPFIA1	2.815	8.45E-25	1.62E-12
Up	FADS1	1.781	7.00E-38	2.01E-02	Up	FADS2	2.214	1.50E-24	2.34E-02
Up	SPP1	1.522	1.24E-37	1.45E-10	Up	DNM1	3.536	1.63E-24	5.64E-03
Up	MMP3	1.762	2.93E-36	1.58E-06	Up	GPR176	2.067	2.15E-24	2.78E-12
Up	PLAU	3.739	7.36e-36	1.62E-12	Up	COL5A2	2.217	3.47E-24	4.95E-04
Up	C10ORF55	2.582	6.41E-34	1.63E-12	Up	CD276	4.029	3.63E-24	1.35E-06
Up	TUBB3	1.857	6.37E-34	5.76E-03	Up	HOXD10	3.591	4.06E-24	1.11E-16
Up	LRP12	2.614	4.15E-33	2.78E-04	Up	SERPINH1	4.046	4.06E-24	3.55E-05
Up	PLXNA1	2.281	1.82E-32	2.56E-06	Up	ZFP64	1.925	4.60E-24	9.48E-08
Up	B4GALNT1	1.664	2.24E-32	3.38E-09	Up	TCOF1	2.541	5.59E-24	2.13E-08
Up	IL24	2.443	6.43E-32	5.84E-05	Up	STIL	4.401	7.33E-24	1.62E-12
Up	COL1A1	1.945	7.68E-31	2.39E-07	Up	MFAP2	2.399	9.32E-24	3.61E-13
Up	TGFBI	2.037	1.35E-30	6.20E-08	Up	APLN	4.296	1.70E-23	8.67E-09
Up	BCL7A	2.315	3.99E-30	9.37E-08	Up	TDO2	4.206	2.01E-23	1.67E-12
Up	UCHL1	3.301	6.66E-30	3.83E-04	Up	CHST1	2.215	2.62E-23	2.01E-11
Up	ARTN	5.896	1.42E-29	4.21E-02	Up	HOXC13	5.05	3.62E-23	3.73E-09
Up	BGN	1.741	3.29E-29	2.98E-02	Up	PGF	2.699	6.38E-23	3.16E-08
Up	STK3	1.165	4.01E-29	3.62E-04	Up	COL1A2	4.419	4.40E-22	1.76E-02
Up	FADS3	1.623	8.73E-29	2.36E-03	Up	ANO1	2.264	5.51E-22	7.47E-09
Up	TNC	1.837	1.16E-28	7.93E-08	Up	MAD2L2	2.376	6.00E-22	1.54E-12
Up	ADAMTS12	1.672	1.41E-28	5.21E-12	Up	SH2D5	2.193	6.07E-22	1.80E-03
Up	MMP13	3.435	1.81E-28	1.42E-04	Up	PYCR2	4.741	6.34E-22	5.44E-11
Up	MMP11	4.269	4.28E-28	1.62E-12	Up	CTHRC1	4.347	2.25E-30	<1E-12
Up	LAMC2	4.48	6.00E-28	6.99E-15	Up	CDC25B	2.392	4.16E-37	<1E-12
Up	MMP10	2.501	7.07E-28	2.13E-05	Up	MCM2	2.523	3.52E-27	<1E-12
Up	OSM	2.703	7.30E-28	2.20E-06	Up	KIF26B	3.511	2.60E-24	<1E-12
Up	ADCY3	5.062	9.28E-28	1.14E-02	Up	ECT2	2.516	1.17E-23	<1E-12
Up	FAP	1.801	1.25E-27	2.48E-03	Down	KAT2B	-7.185	1.49E-41	1.02E-02
Up	FCGR2A	1.893	2.94E-27	1.36E-04	Down	UBL3	-5.361	4.54E-38	1.43E-04
Up	UAP1L1	2.312	3.40E-27	1.63E-12	Down	NUCB2	-4.728	1.76E-34	2.23E-02
Up	TNFAIP6	3.426	6.36E-27	2.90E-02	Down	CAB39L	-4.833	1.10E-31	1.65E-02
Up	ABL2	1.846	1.43E-26	2.98E-02	Down	PAIP2B	-6.092	5.96E-24	3.30E-03

Type	Gene	Log2 (fold-change)	P value (GEO)	P value (TCGA)	Type	Gene	Log2 (fold-change)	P value (GEO)	P value (TCGA)
Up	SHOX2	2.895	1.93E-26	1.51E-08	Down	GCOM1	-2.019	2.90E-23	1.39E-02
Up	MMP12	1.612	2.25E-26	1.70E-10	Down	HPGD	-2.293	6.77E-23	3.03E-02
Up	LIMK1	2.181	3.68E-26	7.53E-10	Down	LGALS3	-6.284	2.42E-22	1.37E-02

** The columns of 'Type' indicates up-regulated (Up) and down-regulated (Down) gene expression. The column 'Log2(foldchange)' indicates the result of log2(mean(cancerous group)/ mean(adjacent normal group)) from the GEO dataset. The p values indicate the statistical significance of t-tests in the GEO and TCGA datasets, respectively*

3.2 Result of Functional Enrichment Analysis

To investigate what functions, such as biological processes (BPs) based on GO (Gene Ontology) and signaling pathway based on KEGG (Kyoto Encyclopedia of Genes and Genomes), these DEGs were mainly involved in, I performed a functional enrichment analysis. As shown in Table 2, then significantly enriched functions included extracellular matrix organization, collagen fibril organization, cell adhesion and signaling transduction, and so on. Several KEGG pathway was also significantly enriched in the DEGs, such as extracellular matrix (ECM)-receptor interaction, focal adhesion and PI3K-Akt signaling pathway, and so on (Table 2).

Table 2. – *Result of DAVID functional enrichment analysis*

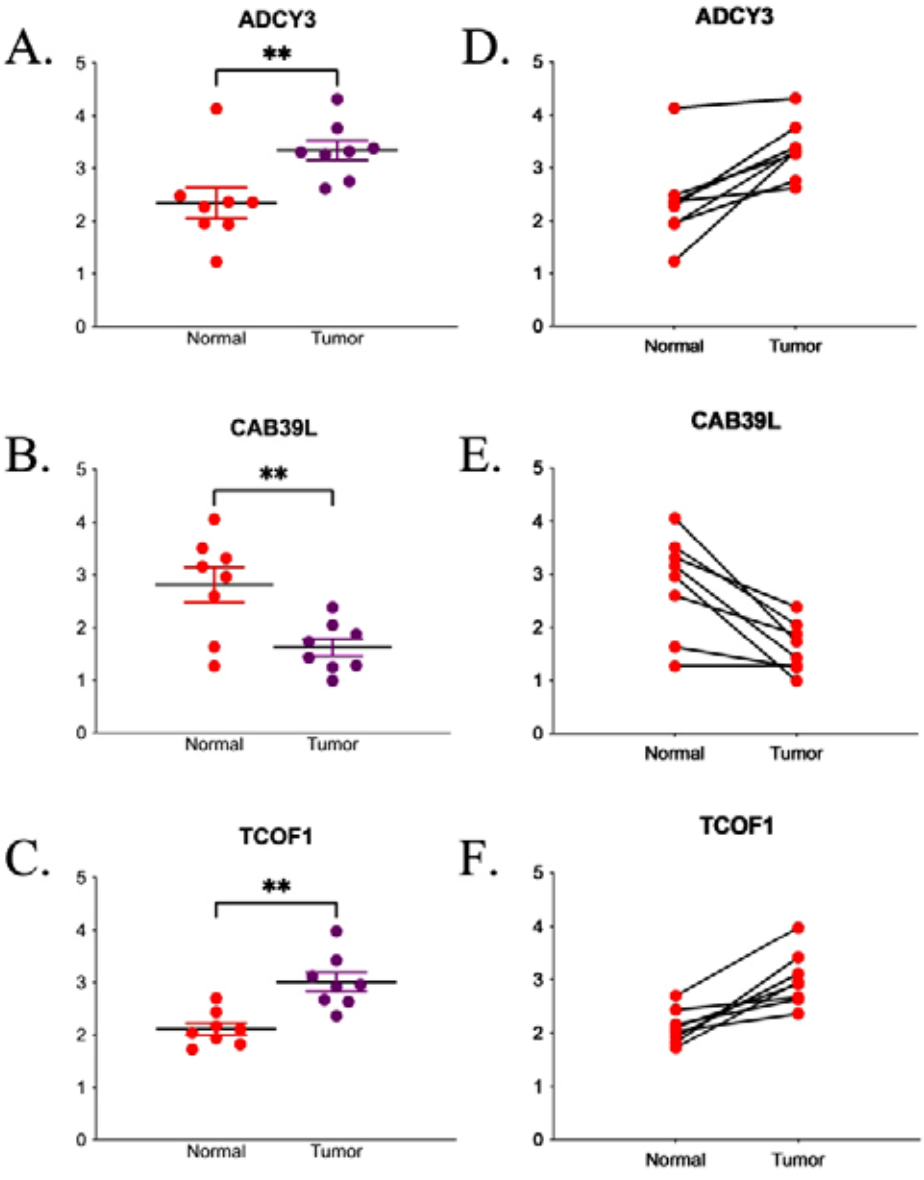
Term	P value	Gene
GO:0030198~extracellular matrix organization	3.62E-08	MMP12, COL1A1, MMP11, MMP13, COL1A2, COL5A2, MMP3, TGFBI, ADAMTS12, MMP10
GO:0030199~collagen fibril organization	1.05E-05	COL1A1, MMP11, COL1A2, COL5A2, SERPINH1, ADAMTS12
GO:0030574~collagen catabolic process	1.77E-05	MMP12, MMP11, MMP13, MMP3, MMP10
GO:0022617~extracellular matrix disassembly	2.81E-05	MMP12, MMP11, MMP13, MMP3, MMP10
GO:0006508~proteolysis	2.01E-04	MMP12, MMP11, MMP13, FAP, PLAU, ADAM12, MMP3, ADAMTS12, MMP10
GO:0007165~signal transduction	3.05E-04	TNFAIP6, IL24, LIMK1, ADCY3, PGF, MAPK12, STK3, APLN, PLAU, ARTN, CHN1, SPP1, PPFIA1, ABL2, LRP12
GO:1904645~response to beta-amyloid	1.27E-03	MMP12, MMP13, MMP3
GO:0007155~cell adhesion	1.34E-03	COL1A1, TNFAIP6, FAP, ADAM12, SPP1, TNC, ABL2, LAMC2, TGFBI
GO:0001649~osteoblast differentiation	1.41E-03	COL1A1, SHOX2, SPP1, TNC, CTHRC1
GO:0006636~unsaturated fatty acid biosynthetic process	1.46E-03	FADS3, FADS2, FADS1
GO:0001501~skeletal system development	1.72E-03	COL1A1, COL1A2, TCOF1, COL5A2, SHOX2
GO:0035556~intracellular signal transduction	8.09E-03	CAB39L, CHN1, ADCY3, ECT2, MAPK12, STK3, GCOM1

Term	P value	Gene
hsa04512: ECM-receptor interaction	1.12E-03	COL1A1, COL1A2, SPP1, TNC, LAMC2
hsa04611: Platelet activation	3.79E-03	COL1A1, FCGR2A, COL1A2, ADCY3, MAPK12
hsa04510: Focal adhesion	3.83E-03	COL1A1, COL1A2, SPP1, TNC, LAMC2, PGF
hsa04926: Relaxin signaling pathway	4.36E-03	COL1A1, MMP13, COL1A2, ADCY3, MAPK12
hsa04151: PI3K-Akt signaling pathway	9.44E-03	COL1A1, COL1A2, OSM, SPP1, TNC, LAMC2, PGF

3.3 Paired cancer and para-cancer analysis reveals new ESCA related genes

The GEO dataset mentioned above includes 46 paired cancerous and non-cancerous (or para-cancerous) tissues from 23 patients, whereas the TCGA dataset was derived from cancerous tissues of 184 samples and only 11 non-cancerous tissues of 11 samples.

Figure 1. *Differential expression of the three genes between the normal and cancerous tissues of ESCA*



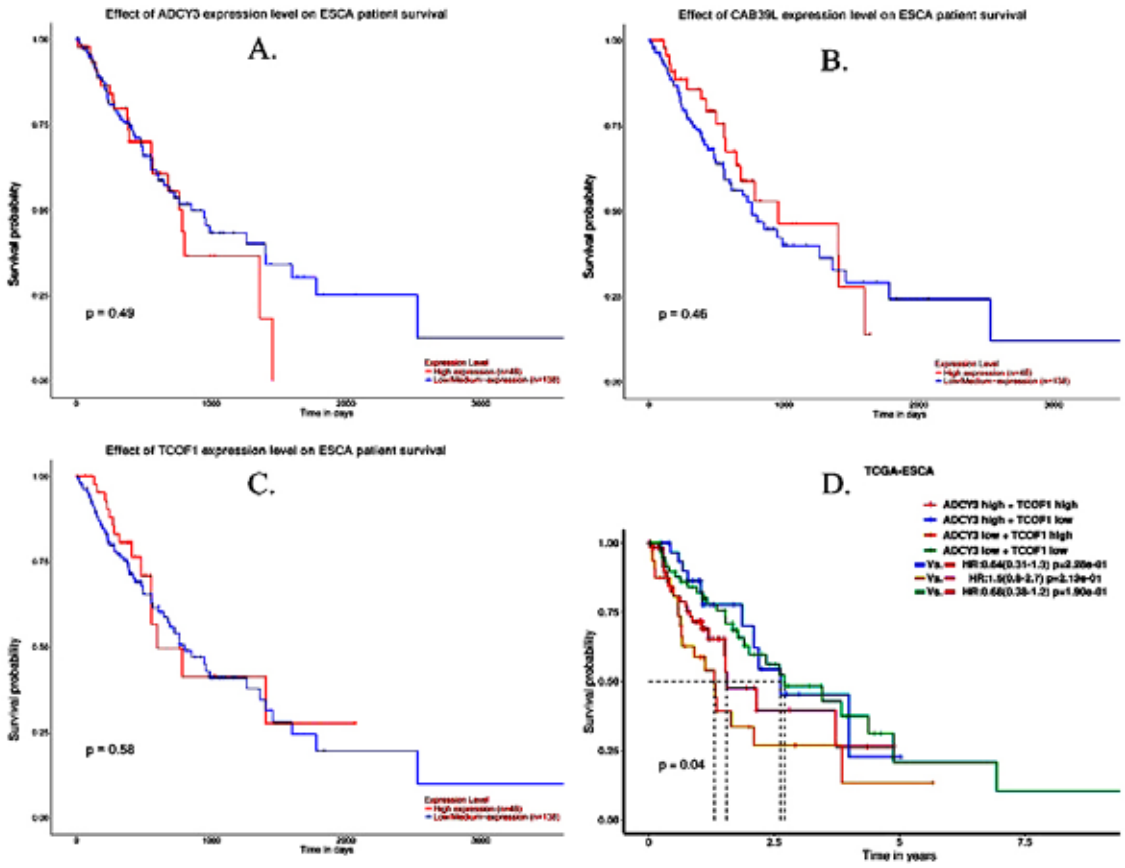
For the TCGA dataset, there were a total of 16 paired cancerous and non-cancerous tissues from 8 patients. Therefore, the total 42 genes involved in the enriched functions in Table 2 were further checked for the differential expression using the paired TCGA data. As a result, 32 genes were found to be significantly different comparing esophageal cancerous and the adjacent normal gene expression after *t*-test on the 42 genes we got from functional enrichment analysis. Between 32 genes, three new genes including adenylate cyclase 3 (ADCY3), calcium-binding protein 39 (CAB39L), and treacle ribosome biogenesis factor 1 (TCOF1) have not been published related to ESCA. Therefore, we focused on the three genes for the next analysis. Among the genes, ADCY3 and TCOF1 were up-regulated, whereas CAB39L was down-regulated (Figure 1).

The x-axes indicate groups of categories, while the y-axes indicate relative expression levels. The stars indicate statistical significance: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Differential expression of three genes including ADCY3 (A, D), CAB39L (B, E), TCOF1 (C, F) between the normal and cancerous tissues of each individual ESCA patients are shown. The lines in D, E and F indicate the paired cancerous and adjacent normal tissues of the same patients.

3.4 Survival Analysis

Next, I investigated the clinical significance of the three genes and performed the survival analysis based on the overall survival (OS) of patients with different expression levels of the genes. The survival analysis model was built on those three genes (ADCY3, CAB39L, TCOF1) individually at first (Figure 2). However, there was no impact of individual gene on the survival probability (Figure 2, A, B & C). Therefore, the survival probability of combinations of pairing those three genes with each other was analyzed using the online ToPP server. The results revealed that the OS based on the combination of ADCY3 and TCOF1 showed a statistical significance (p-value lower than 0.05) in the survival probability impact on ESCA (Figure 2, D). However, other combinations did not show any significant difference of OS among different combined groups (data not shown).

Figure 2. *Survival probability model for the indicated three genes*



The results of survival analysis based on the single gene of ADCY3 (A), CAB39L (B) and TCOF1 (C), as well as the combination of ADCY3 and TCOF1, are shown. Combination of ADCY3 and TCOF1 (D) is the Survival probability model for the combination of expression of ADCY3 and TCOF1 over 2.5-, 5-, 7.5-, 10-years.

4. Discussion

Three new genes (ADCY3, CAB39L, TCOF1) associated with development ESCA are identified in the research. Based on current study, ADCY3 is associated with obesity (Saeed, et al., 2018). Mutated ADCY3 will increase the risk of type two diabetes and mutated ADCY3 is a type of genetic disease (Grarup, et al., 2018). According to previous studies, CAB39L often possessed diagnostic and prognostic values and tumor suppressor in several types of cancer, including kidney renal clear cell carcinoma (KIRC), gastric cancer (GC), and colorectal cancer (CRC) (Wu, et al., 2023; Li et al., 2018; Choi, et al., 2016). Existing studies shows that TCOF1 is a nucleolar factor regulated ribosomal DNA (rDNA) transcription in nucleolus (Wu, et al., 2022). TCOF1 can leads to disorder like Treacher Collins Syndrome (TCS), hepatocellular carcinoma (HCC) (Marszałek-Kruk, et al., 2021).

Though three new genes may contribute to the development of esophageal tumor, there is potential drawback in my research. In my study, the simple size of my experiment is not very big, though two different datasets were used. In addition, there is inadequate in research in my experiment. The current analysis is mainly based on bioinformatics analysis, the specific molecular mechanism of the three genes needs further investigation. Moreover, differential expression can be detected at protein level using clinical samples to confirm the DEGs identified at mRNA level.

5. Conclusions

Three new DEGs (ADCY3, CAB39L, TCOF1) of ESCA were identified, providing novel insight for potential mechanism of the oncogenesis and development of ESCA. They could be served as candidates for drug targets and/or biomarker for prognostic analysis and provide new attention for medical workers to make better clinical decisions, treatment strategies for ESCA patients and for researcher to conduct further experiment.

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