

Authentication of Differential Gene Expression in Oral Squamous Cell Carcinoma using Machine Learning Applications

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Research Article

Keywords: The Cancer Genome Atlas, oral squamous cell carcinoma, convolutional neural network, tumour classification, diagnostic model

Posted Date: December 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-128045/v1>

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Abstract

Background: Recently, the possibility of tumour classification based on genetic data has been investigated. However, genetic datasets are difficult to handle because of their massive size and complexity of manipulation. In the present study, we examined the diagnostic performance of machine learning applications using imaging-based classifications of oral squamous cell carcinoma (OSCC) gene sets.

Methods: RNA sequencing data from SCC tissues from various sites, including oral, non-oral head and neck, oesophageal, and cervical regions, were downloaded from The Cancer Genome Atlas (TCGA). The feature genes were extracted through a convolutional neural network (CNN) and machine learning, and the performance of each analysis was compared.

Results: The ability of the machine learning analysis to classify OSCC tumours was excellent. However, the tool exhibited poorer performance in discriminating histopathologically dissimilar cancers derived from the same type of tissue than in differentiating cancers of the same histopathologic type with different tissue origins, revealing that the differential gene expression pattern is a more important factor than the histopathologic features for differentiating cancer types.

Conclusion: The CNN-based diagnostic model and the visualisation methods using RNA sequencing data were useful for correctly categorising OSCC. The analysis showed differentially expressed genes in multiwise comparisons of various types of SCCs, such as *KCNA10*, *FOSL2*, and *PRDM16*, and extracted leader genes from pairwise comparisons were *FGF20*, *DLC1*, and *ZNF705D*.

Introduction

Traditionally, the choice of treatment modality for cancer primarily depends on the histopathologic diagnosis, and a definite diagnosis plays a major role in choosing a treatment strategy and determining the prognosis of the disease [1, 2]. Thus, though the importance of an accurate diagnosis of cancer is substantial, studies on the development of new classifications of tumour types are rare, and current classification schemes primarily depend on the morphologic characteristics of tumour cells and tissues [3, 4]. However, there are numerous examples of cancers with the same diagnostic classification (based on similar histopathologic features) having different responses to therapies. These differences result from alterations of the biological behaviour of cancer cells via genetic variations as well as environmental factors [5–7]. Thus, a diagnostic model that predicts the biological behaviour of cancers by considering their genetic characteristics rather than only morphologic characteristics needs to be developed.

Understanding the genetic heterogeneity of cancers can provide clues for increasing diagnostic accuracy and developing efficient biomarkers as well as improving treatment efficacy [8–11]. A massive amount of cancer tissue genomic data have been generated due to the development of next-generation sequencing methods with high efficiency and accuracy, and most of the data are housed by The Cancer Genome

Atlas (TCGA) database [12–14]. Using RNA sequencing expression data, studies have attempted to find a diagnostic model that can efficiently and rapidly discriminate different tumours by simultaneously considering both genetic phenotypic features [15–17]. Due to the difficulty in manually interpreting genomic datasets, various machine learning methods that are trained on differentially expressed gene sets across tumours have been used to analyse and classify tumours based on tumour-specific gene expression [18]. However, using generic machine learning methods such as genetic algorithms yields high dimensionality of the genomic dataset, and innovative methods are continuously being developed to increase performance. Recently, Lyu et al developed a more efficient method by applying convolutional neural network (CNN) image classification, which is a state-of-the-art method for solving classification problems [19]. In addition, deep learning methods exploiting image classification/recognition have been suggested, and these methods have displayed excellent performance as well as a low error rate [17, 20]. Using methods such as these, tumour classifications based on machine learning analysis of genetic data have been rapidly developed and tested. However, research to establish a classification system to diagnose oral squamous cell carcinoma (OSCC) using genetic data is rare.

OSCC, the most common cancer of the oral cavity, derives from the oral mucosa (which is lined by stratified squamous epithelium) and shares morphologic findings and histochemical features with SCC of other sites or tissues. All SCCs are diagnosed as the same type of disease due to similar histologic findings, but the gene expression of each SCC has not been compared. Therefore, it is not well understood whether the genetic features of SCCs of various tissues or organs are similar. Knowledge of the genetic features distinguishing OSCC from SCCs of other tissues might provide clues for differential diagnosis and the development of treatment paradigms. In the present study, we examined the diagnostic performance of machine learning applications using CNN image classification for OSCC samples. In addition, we investigated the differences in genetic features between OSCC and other types of SCC, which may provide a basic rationale for potential diagnostic models and the development of targeted therapy.

Methods

Data procurement

RNA sequencing data from samples of OSCC, non-oral head and neck SCC (HNSCC), oesophageal SCC, oesophageal adenocarcinoma, and cervical SCC were downloaded from the TCGA database (<http://cancergenome.nih.gov/>). The platforms used, experiment types, and numbers of samples analysed for mRNA expression for each cancer are shown in Table S1.

Computational analysis

The workflow of our study is shown in Fig. 1. The feature extraction for differentiating SCCs based on gene expression was performed using the protocol in reference with a few modifications and consists of 4 steps: 1) data preprocessing, 2) differentiation using CNN [21, 22], 3) heatmap generation, and 4) feature extraction. The 4 steps are briefly explained below, and the detailed methods for CNN and heatmap generation are described in the following sections.

1) Data preprocessing

To cope with high-dimensional expression data, the RNA sequencing data of the TCGA dataset were embedded into 1-D images. Briefly, the normalised read count data of each gene with enormous values were transformed by using $y = \log_2(x + 1)$, and noise data were filtered out by using a variance threshold of 1. Then, the data were embedded into 1-D images.

2) Differentiation

The differentiation step used the CNN model to process the 1-D images output from the preprocessing step. The training and testing were performed using a 10-fold cross validation method.

3) Heatmap generation

The class activation map method was used to visualise what the CNN had learned and heatmap images representing the contribution of each gene were produced from the image input.

4) Feature extraction

Since each pixel corresponds to one gene, feature extraction methods take the most important pixels with the most intensity within the image and categorise the corresponding represented genes into a list of dominant genes.

CNN analysis

A CNN model [21, 22], which has multiple layers consisting of three convolutional layers and four fully connected layers, was implemented in this experiment. The first convolutional layer 'conv1' contained 64 different filters, while the second convolutional layer 'conv2' and the third convolutional layer 'conv3' contained 128 and 256 filters, respectively. Both a max-pooling layer and a batch-normalisation layer immediately followed each convolutional layer. A drop-out layer was added before entering the fully connected layer, and the drop-out rate was 25%. The sizes of the three fully connected layers were 36,864, 1,024, 512, and 256. We chose the cross-entropy method as a loss function and the Adam optimiser to update the weights. We used a 10-fold cross validation method to train the CNN and to test the performance.

CNN visualisation

Because we needed to extract features learned through CNN analysis, we employed the class activation map (CAM) method to visualise the learned features from the CNN output. The CAM method helps understand what regions of an input image influence the CNN's output prediction. The technique relies on the generation of a heatmap for visualisation, which highlights pixels of the image that trigger the model to associate the image with a particular class. In this experiment, since each pixel represented a corresponding gene, the CAM method could visualise which gene was dominant for each type of cancer.

Results

The diagnostic tool using machine learning computational analysis exhibited excellent performance in the diagnosis of OSCC but had limited utility differentiating OSCC from non-oral HNSCC

To evaluate the performance of the tool in OSCC diagnosis, its performance capabilities, such as test recall, test precision, and test accuracy, were compared using the dataset containing OSCC, non-oral HNSCC, cervical SCC, and oesophageal SCC samples in a multiwise fashion. After repeated training using the dataset, the tool showed ~ 82% test precision and test accuracy in diagnosing SCCs of various origins (Fig. 2A). When the performance of the diagnostic tool was compared in a pairwise way, it showed a much higher accuracy, precision, recall, and F1 score in differentiating between OSCC and oesophageal SCC and cervical SCC than it did when it was compared in a multiwise fashion, suggesting the possibility that this model could be utilised as a diagnostic tool. However, the comparison considering OSCC and non-oral HNSCC exhibited much lower test accuracy as well as other factors, including test precision and training accuracy, suggesting the difficulty of differentiating OSCC from non-oral HNSCC (Fig. 2B). The authors suspect that the problem may be related to the close spatial relationship between the two types of tumours. To define factors responsible for this difference, the performance of the tool in distinguishing oesophageal SCC from oesophageal adenocarcinoma, which is another common cancer in the oesophagus, was analysed. The tool displayed low performance (~ 58%) in distinguishing specific types of oesophageal cancers, whereas the tool showed high discriminatory performance in comparisons of oesophageal SCC with other SCCs even though these SCCs resemble each other histopathologically. In addition, the tool exhibited high performance in discriminating non-oral HNSCC from SCCs of other tissue origins (Fig. 3). The findings suggest that the tool shows better performance in diagnosing cancers of different tissue origins than in discriminating histopathologically different cancers that are derived from the same type of tissue.

Analysis of the diagnostic tool using machine learning classification suggests that a differential pattern of gene expression is a more important factor than histopathologic features for differentiating cancer types.

To clearly determine diagnostic accuracy in differentiating OSCC from SCC of other tissues or organs, a confusion matrix was generated, as shown in Fig. 4. Oesophageal and cervical SCCs were classified correctly at accuracies of 99% and 98%, respectively, and 83% of OSCC was also correctly diagnosed. However, more than half of the non-oral HNSCCs were misclassified as OSCC, and 15% of OSCC were

misclassified as non-oral HNSCC, further confirming the lower efficiency in discriminating OSCC from non-oral HNSCC (Fig. 4).

To further clarify the importance of the origin of cancer cells, the set of differentially expressed genes between oesophageal squamous cell carcinoma (ESCC) and oesophageal adenocarcinoma was compared to that between OSCC and ESCC. Although both OSCC and ESCC share very similar histopathologic features, the machine learning tool differentiated them easily, with only ~ 2% error when discriminating ESCC from OSCC, whereas 38% of ESCCs were misdiagnosed as oesophageal adenocarcinoma (Fig. 5A & B), implying that the gene expression pattern depends more on the site of tumour occurrence than the histopathologic identity and thus that tissue origin is a more important factor in determining tumour characteristics.

To identify valuable genes for diagnosing OSCC, the dominant genes that could discriminate OSCC from other SCCs were extracted through the class activation map feature extraction method in a multiwise manner. In addition, data on the characteristic genes of OSCC were extracted by individually comparing OSCC with other types of SCC in a pairwise manner: comparison 1) between OSCC and non-oral HNSCC, 2) OSCC and cervical SCC, and 3) OSCC and ESCC. Then, the shared genes from each comparison were selected (Table 1). We compared those genes from the extraction methods and found no consistent genes.

Table 1
List of 20 leader genes of OSCC
extracted from machine learning
tumour classification

No.	Gene name	
	multi-wise	pair-wise
1	KCNA10	FGF20
2	FOSL2	DLC1
3	PRDM16	ZNF705D
4	LUZP1	TUSC3
5	PAPOLG	SLC7A2
6	SIPA1L2	LGI3
7	TEX261	NUDT18
8	BCL10	MTUS1
9	NBPF14	PIWIL2
10	LAMC1	STC1
11	ERRFI1	CDCA2
12	PRAMEF20	DOCK5
13	FMO2	TIMM8A
14	GPA33	CENPI
15	PLA2G5	TSPAN6
16	TMEM167B	ARMCX6
17	GRIK3	TCEAL7
18	RPTN	TCEAL5
19	GPBP1L1	NXF3
20	NHLH1	TCEAL6

Discussion

In the present study, we evaluated whether a diagnostic model based on CNN and visualisation methods using RNA sequencing data were useful in correctly recognising OSCC. We observed that there were no problems in differentiating OSCC from oesophageal or cervical SCCs, implying that OSCCs exhibit distinct gene expression from other SCCs and that histopathologic features cannot correctly reflect the

genetic features of cancer cells. However, discrimination of OSCC from non-oral HNSCC was very difficult, and the discriminative ability of the model increased as distance from oral mucosa increased. Although it used a different data processing from ours, a previous study on molecular diagnostic methods using whole transcriptome RNA sequencing data from TCGA showed that oesophageal carcinomas were misclassified as stomach cancers. The model also reported problems in distinguishing cervical cancers of different histopathologic types, such as SCC, adenosquamous carcinoma, and adenocarcinoma [11]. In this study, we also observed that the differential diagnosis of different oesophageal cancers was limited; for example, distinguishing SCC from adenocarcinoma was difficult even though the two cancers exhibit completely different morphologic features. All these findings suggest that the origin site or organ system of a tumour might be a more important factor in determining genetic variation than histopathologic characteristics, and therefore, a thorough understanding of site-specific genetic changes could provide more useful information and increase diagnostic accuracy. Although their capabilities of differentiating tumour types with the same tissue origin need to be improved for such diagnostic models using genomic data to be clinically applicable, the development of OSCC classification schemes via machine learning algorithms using genomic data on OSCC diagnosis is promising given the confirmed ability to distinguish OSCC from other types of SCC found in this study. In addition, the findings strongly imply that information on tissue origin-based genetic variations could contribute to more effective therapeutic targets for cancer.

Through the process of computational analysis for developing diagnostic models in this study, we were able to identify a set of genes with differential expression relevant to SCCs. Interestingly, the extracted genes were completely different depending on the analytical method used. For example, a single groupwise comparison among all types of SCCs indicated *KCNA10*, *FOSL2*, and *PRDM16* as the top 3 candidates useful for the diagnosis of OSCC, whereas *FGF20*, *DLC1*, and *ZNF705D* were extracted as leader genes from pairwise comparisons. Furthermore, no genes characteristic of OSCC overlapped among the top 20 candidates extracted using the two different comparative methods. The exact source of such difference remains unclear, but the diverse sets of candidate genes derived from each analysis were likely to play a role. For instance, it is plausible that the commonly shared genes in all SCC types are often excluded from the final list of candidates in a single-grouped analysis, leaving only those with differential expression to be further considered. In contrast, the candidates more relevant to the identity of affected tissues in each SCC appear more likely to be extracted from pairwise comparisons, in line with the significant influence of tissue proximity on the genomic profiles relevant for the diagnosis of various SCCs. These discrepancies may raise a concern when bioinformatical analyses based upon widely variable control and tissue types are generally applied either to develop common diagnostic biomarkers or to identify shared therapeutic targets for the treatment of cancers with similar pathology. The diverse sets of genes extracted from different analytical methods in this study may further implicate the need for multifaceted analyses of genomic profiles relevant to a specific type of cancer, such as OSCC. The development of optimised analytical means awaits further biological and experimental investigations in the future.

In addition, a previous study using the TCGA and Gene Expression Omnibus (GEO) databases reported 6 primitive biomarkers of OSCC (*GNA14*, *CMA1*, *DKK1*, *HOXC6*, *HCG22*, and *HOTTIP*) that were not found in our results [13]. This discrepancy may be due to differences in the targets being compared. The study of Huang et al. identified genes by comparing gene expression profiles of OSCC tissue and normal controls, whereas we extracted diagnostic markers of OSCC by analysing SCCs of other tissues, and the extracted genes in this study are being reported in this context for the first time. Among the identified genes, *PRDM16* and *DLC1* have been studied in various types of cancers, and the significance of these genes in OSCC has not been examined [23–26]. Furthermore, the roles of *KCNA10* and *ZNF705D* in the pathogenesis of cancer, including OSCC, have not been investigated, suggesting the novel insights gained from this study and new avenues for the diagnosis of and new treatment strategies for OSCC.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The data used for this study comes from The Cancer Genome Atlas database. Detailed information and further explanation about the data source is provided on <https://www.cancer.gov/about-nci/organization/ccg/research/structural-genomics/tcga>. Dataset is publicly available on Broad Institute GDAC Firehose, can be accessed through <https://gdac.broadinstitute.org/>.

Competing interest

None declared

Funding

This study was supported by the Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Science and ICT (NRF No. 2018R1A5A2023879 and NRF No. 2020R1A2C1005203).

Authors' contributions

G. Song, J.J. Hwang, and H.R. Park were involved in the initial conception of the research idea and were joined by R. Pratama and J.H. Lee. G. Song, J.J. Hwang, and J.H. Lee contributed to the experimental design. G. Song and J.J. Hwang provided training and technical assistance and R. Pratama conducted the experiments. G. Song, J.J. Hwang, and H.R. Park analyzed the data. R. Pratama and G. Song provided figures and tables. R. Pratama, J.H. Lee, and H.R. Park wrote the main manuscript text. All authors contributed to the interpretation of results and provided critical feedback that shaped the final article.

Acknowledgment

Not applicable

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Figures

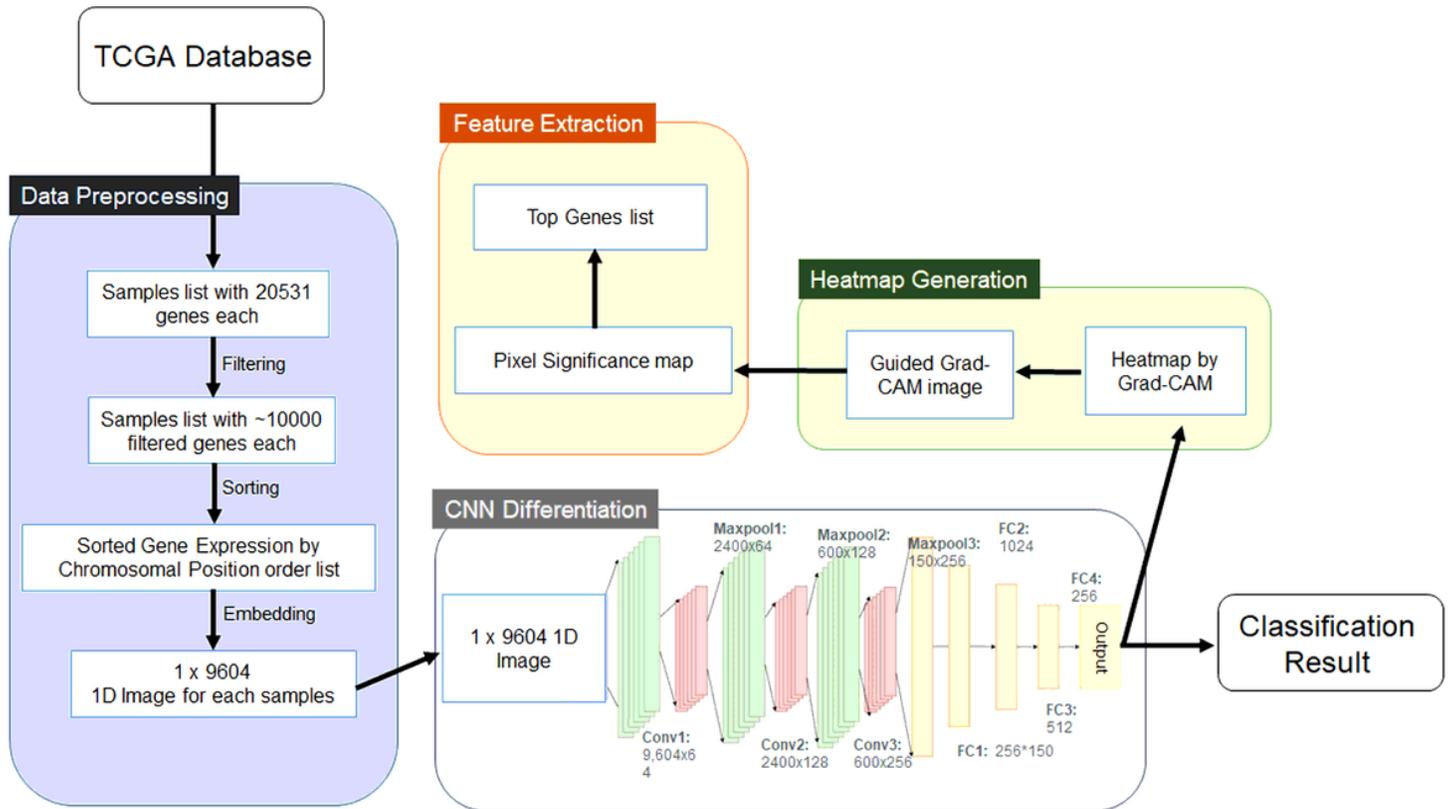


Figure 1

The workflow of this study

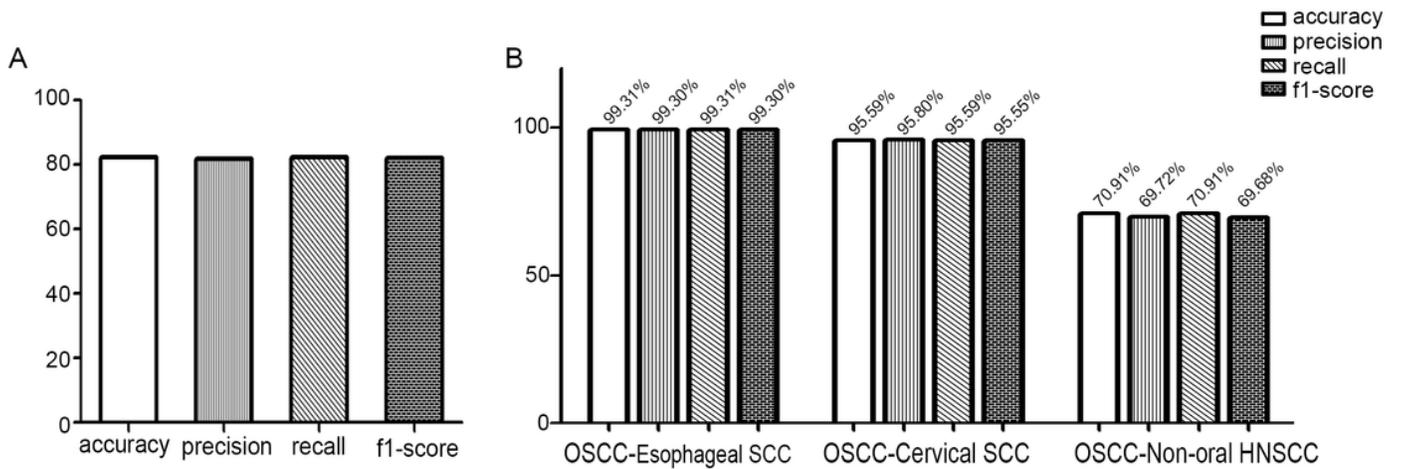


Figure 2

Performances of our method which compared various types of squamous cell carcinoma (SCC) genetic set in multiwise fashion (A) and compared individually oral SCC with other SCC (B).

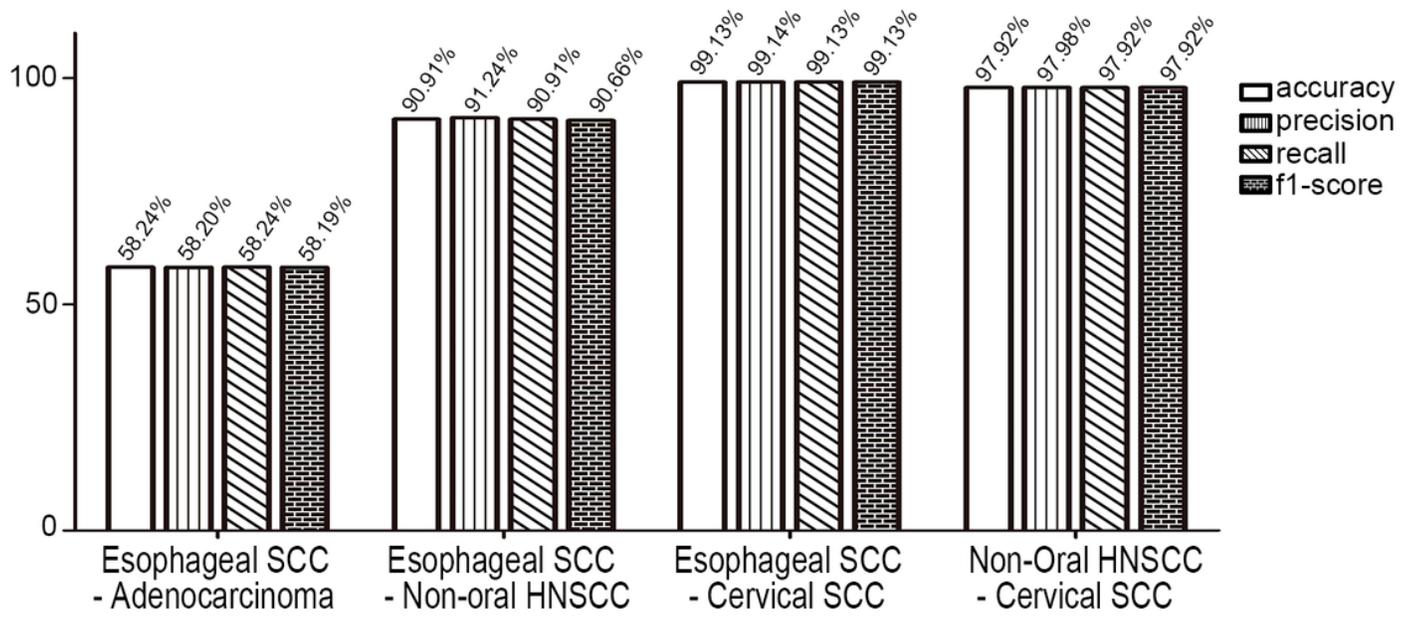


Figure 3

Performances of our method which compared non-oral head and neck SCC with oesophageal using SCC genetic set

Classification Confusion Matrix

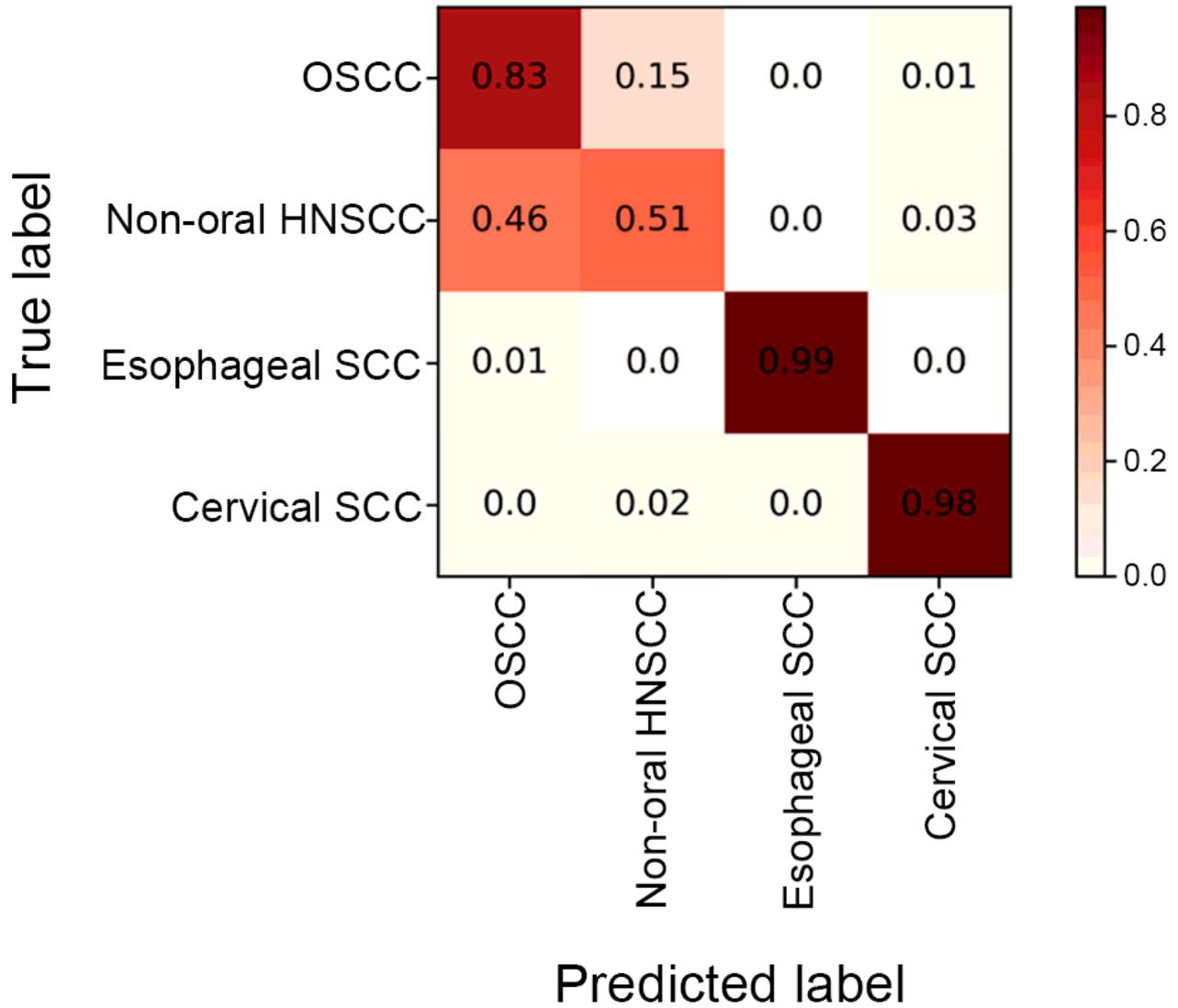


Figure 4

The confusion matrix for classification of SCCs

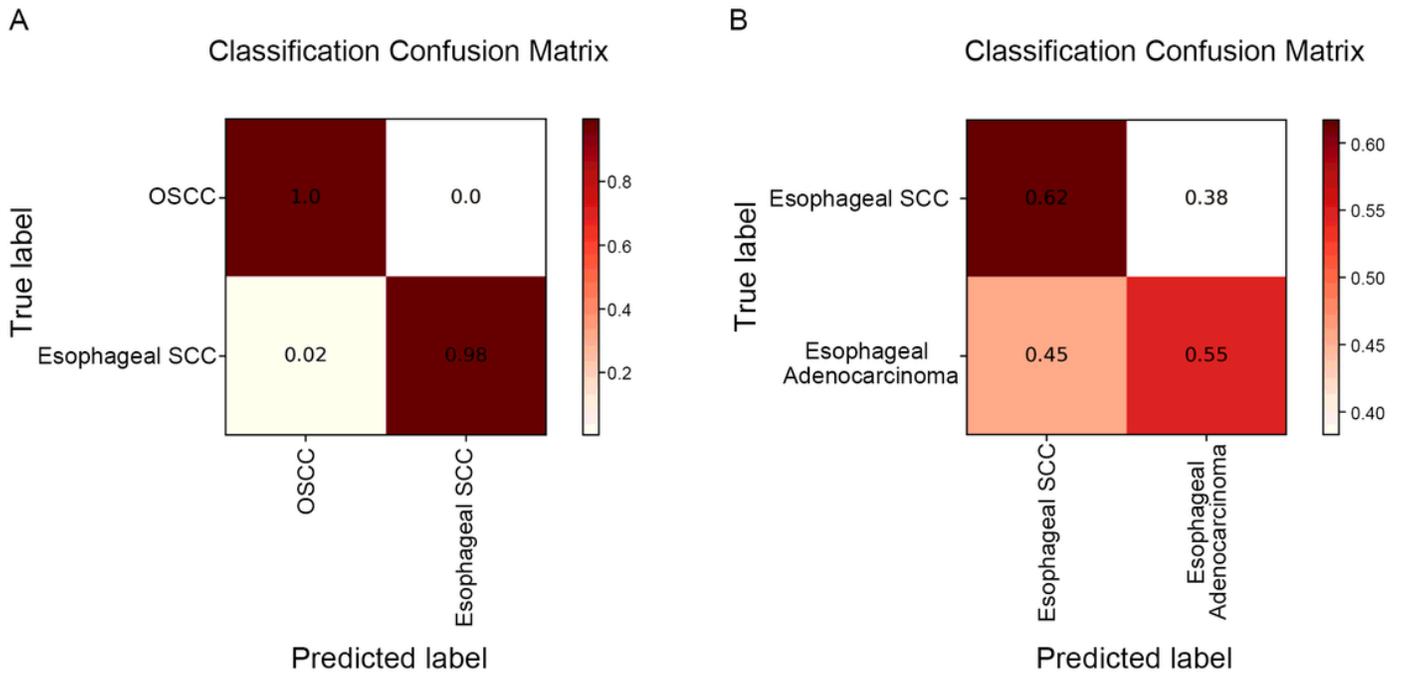


Figure 5

The confusion matrix for differentiation diagnosis of OSCC from oesophageal SCC (A) and of oesophageal cancers (B).

Supplementary Files

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- [TableS1.docx](#)