Hepatocellular carcinoma (HCC) is the most common subtype of liver cancer, and assessing its histopathological grade requires visual inspection by an experienced pathologist. In this study, the histopathological H&E images from the Genomic Data Commons Databases were used to train a neural network (inception V3) for automatic classification. According to the evaluation of our model by the Matthews correlation coefficient, the performance level was close to the ability of a 5-year experience pathologist, with 96.0% accuracy for benign and malignant classification, and 89.6% accuracy for well, moderate, and poor tumor differentiation. Furthermore, the model was trained to predict the ten most common and prognostic mutated genes in HCC. We found that four of them, including CTNNB1, FMM2, TP53, and ZFX4, could be predicted from histopathology images, with external AUCs from 0.71 to 0.89. The findings demonstrated that convolutional neural networks could be used to assist pathologists in the classification and detection of gene mutation in liver cancer.
Herein, based on the inception V3 network developed by Google and some packaging code from Coudray et al. via EASY DL platform and whole-slide images (WSIs) of H&E stained liver tissue, we have established a model to classify liver tissue and predict certain gene mutations. The model was externally validated by an independent cohort.

RESULTS

The distribution of WSIs and tiles

There were 491 WSIs of H&E stained liver tissue from the Genomic Data Commons portal (GDC-portal, https://portal.gdc.cancer.gov/), including 402 WSIs of HCC and 89 WSIs of normal liver tissue. The information on histopathological grade was not available in 19 of 402 WSIs of HCC. According to the histopathological grade, they were then sorted into well (G1, n = 55), moderate (G2, n = 187), and poor group (G3/G4, n = 141) in the remaining 383 WSIs of HCC. A total of 387 WSIs of HCC with corresponding gene mutation information were available. Besides, 67 WSIs of HCC with histopathological grade and related gene mutation information were available. Similarly, 67 WSIs of HCC were selected from Sir Run-Run Shaw Hospital (SRRSH). After each WSI was cropped into small and 34 WSIs of normal liver tissue were selected from SRRSH. The distribution of WSIs and tiles in each subset is shown in Table 1. The high-performance level of our models at recognizing tumors from normal liver tissue (AUC = 0.961; 95% CI 0.939–0.981) was observed in the validation set (Fig. 2a). Based on the class-imbalanced problem, the precision-recall curves (PR-curves) and Matthews correlation coefficient (MCC) were also used to evaluate its performance (Fig. 2b). The MCC was up to 0.82 for benign or malignant classification, and 0.738 for assessing histopathological grade (well, moderate, or poor). Compared to three pathologists with 2-year, 5-year, and 10-year experience in respective, the performances of our classifiers nearly reached the ability of pathologists with 5-year experience (Table 2).

Performance of classification

Our models were trained and validated based on the ten most significantly mutated genes to estimate the possibility of mutation. The performances, including accuracy, precision, and recall rate, F1-score, and MCC, were summarized in Table 3. In order to reduce heterogeneity, the performance was assessed both the average predicted probability on region (tiles)-level and the probability of predicted tile (P > 0.5) on slide-level in the external validation set. On the region(tiles)-level, we found that five of which, including ARID1A (P = 0.036), CTNNB1 (P < 0.0001), FAM2 (P = 0.0003), TP53 (P = 0.0011) and ZFX4 (P = 0.0054), showed significant differences between mutation and wild type group (Fig. 3a), with the area under the receiver operating characteristic (AUC) of 0.738.

Table 1. The distribution of patients, histopathological images/WSIs, and tiles in each subset.

| Patients | Histopathological images | Tiles |
|----------|--------------------------|-------|
|          | Tr | Te | IV | EV | Tr | Te | IV | EV | Tr | Te | IV | EV |
| Normal and HCC | | | | | | | | | | | | |
| HCC | 208 | 41 | 128 | 67 | 225 | 47 | 130 | 67 | 41,578 | 8157 | 24,294 | 13,393 |
| Normal | 53 | 9 | 27 | 34 | 53 | 9 | 27 | 34 | 12,614 | 2204 | 9493 | 7863 |
| Histopathological grade | | | | | | | | | | | | |
| Well (G1) | 31 | 7 | 14 | 17 | 33 | 8 | 14 | 17 | 6967 | 1893 | 2654 | 3199 |
| Moderate (G2) | 98 | 17 | 60 | 38 | 106 | 20 | 61 | 38 | 18,754 | 3862 | 10,953 | 7801 |
| Poor (G3/G4) | 69 | 14 | 48 | 12 | 76 | 16 | 49 | 12 | 13,701 | 3189 | 8783 | 2393 |
| CTNNB1 mutation | | | | | | | | | | | | |
| Yes | 60 | 13 | 26 | 21 | 63 | 15 | 26 | 21 | 11,283 | 3218 | 5329 | 4120 |
| No | 142 | 29 | 96 | 46 | 153 | 32 | 98 | 46 | 28,437 | 6321 | 18,342 | 9273 |
| FAN2 mutation | | | | | | | | | | | | |
| Yes | 31 | 7 | 9 | 10 | 32 | 7 | 9 | 10 | 6335 | 1632 | 2143 | 2736 |
| No | 171 | 35 | 113 | 57 | 184 | 40 | 115 | 57 | 34,103 | 7963 | 20,754 | 10,657 |
| TP53 mutation | | | | | | | | | | | | |
| Yes | 64 | 14 | 42 | 20 | 68 | 14 | 43 | 20 | 12,537 | 2873 | 7794 | 4341 |
| No | 138 | 28 | 80 | 47 | 148 | 33 | 81 | 47 | 26,521 | 6359 | 16,646 | 9052 |
| ZFX4 mutation | | | | | | | | | | | | |
| Yes | 35 | 5 | 20 | 15 | 36 | 6 | 20 | 15 | 7273 | 1468 | 3892 | 3224 |
| No | 167 | 37 | 102 | 52 | 180 | 41 | 104 | 52 | 33,219 | 7845 | 19,233 | 10,169 |

Tr training subset, Te test subset, IV internal validation subset, EV external validation subset.
operating characteristic curves (AUCs) from 0.71 to 0.89 in the external validation set. In addition, similar differences were observed on the slide-level, except for ARID1A (Fig. 3b). The per-slide AUCs after aggregation by average predicted probability and percentage of tiles with positive classification were listed in Table 4.

DISCUSSION
In this study, the deep-learning classifiers displayed a high-level performance at recognizing cancer apart from normal liver tissue and assessing histopathological grade (well, moderate, or poor). The performances nearly reached the ability of pathologists with 5-year experience. Interestingly, the model found 9 out of 13 WSIs

Fig. 2 The performance of the model at automated recognizes tumors from normal liver tissue. a The receiver operating characteristic curve. TPR represents true positive rate, and FPR represents false positive rate. b Precision-recall curve.

Fig. 1 Deep-learning framework for training and evaluating the model to classify and predict mutation. Patients from TCGA were randomly divided into training cohorts (training and test) and internal validation cohort. Some patients had multiple virtual slides, and each slide was sliced into smaller “tiles”. The training, test, and internal and external validation sets were made up of multiple tiles from related cohorts. Model selection was done based on the performance in the test set. After learning and selection, the model was applied to tiles in the internal and validation sets to assess their performances.
Table 2. The performance of our models and pathologists’ ability for classification.

| Classifiers | Performance Our models Pathologists with different years’ experience | 2-year | 5-year | 10-year |
|-------------|-------------------------------------------------------------|--------|--------|---------|
| Normal vs. tumor | Accuracy | 0.960 | 0.911 | 0.970 | 0.990 |
|             | Precision | 0.945 | 0.926 | 0.957 | 0.985 |
|             | Recall | 1.000 | 0.940 | 1.000 | 1.000 |
|             | F1-score | 0.971 | 0.933 | 0.978 | 0.993 |
|             | MCC | 0.912 | 0.799 | 0.934 | 0.977 |
| Well (G1) vs. moderate(G2) vs. poor (G3/ G4) | Accuracy | 0.896 | 0.851 | 0.910 | 0.955 |
|             | Precision | 0.879 | 0.831 | 0.869 | 0.944 |
|             | Recall | 0.771 | 0.758 | 0.807 | 0.895 |
|             | Micro F1-score | 0.820 | 0.754 | 0.836 | 0.914 |
|             | MCC | 0.738 | 0.637 | 0.764 | 0.882 |

MCC: Matthews correlation coefficient. *Average value.

Table 3. The performances of our models for gene mutation prediction.

| GENE | Accuracy | Precision | Recall | F1-score | MCC |
|------|----------|-----------|--------|----------|-----|
| ARID1A | 0.925 | 0.833 | 0.769 | 0.800 | 0.755 |
| ASH1L | 0.896 | 0.778 | 0.583 | 0.667 | 0.615 |
| CSMD1 | 0.910 | 0.714 | 0.556 | 0.625 | 0.581 |
| CTNNB1 | 0.910 | 0.895 | 0.810 | 0.850 | 0.788 |
| EYS | 0.925 | 0.800 | 0.500 | 0.615 | 0.596 |
| FMN2 | 0.925 | 0.727 | 0.800 | 0.762 | 0.719 |
| MDM4 | 0.925 | 0.750 | 0.429 | 0.545 | 0.532 |
| RB1 | 0.940 | 0.800 | 0.571 | 0.667 | 0.646 |
| TP53 | 0.925 | 0.895 | 0.850 | 0.872 | 0.820 |
| ZFX4 | 0.910 | 0.846 | 0.733 | 0.786 | 0.732 |

MCC: Matthews correlation coefficient.

from our center with grading misclassified by at least a pathologist. Although the sensitivity and accuracy still need to be improved to be on par with a 10-year experience pathologist, it could be used to assist young pathologists at diagnosing with shorter learning curve period, faster speed, and higher accuracy. Moreover, the prediction of the four genes mutation (CTNNB1, FMN2, TP53, and ZFX4) is beyond the ability of pathologists.

The prediction of mutation based on histopathological H&E images using deep learning may have a positive influence on the diagnosis and treatment of patients with cancer given the importance of gene mutation. For example, the mutations in CTNNB1 occurred at a relatively high frequency in HCC, with a high expression of the protein kinase human monopolar spindle 1 (hMps1/TTK), and TTK inhibitors regarded as one of the potential targeted drugs for CTNNB1 mutant HCC. Interestingly, our models showed a high-performance level of predicting CTNNB1 mutation. The prediction of CTNNB1 mutation using deep learning may make a great contribution to select patients who are most likely to respond to TTK inhibitor targeted therapy.

Due to the unclear AI algorithmic data processing in a “black box”, developers and users do not know how computers arrive at conclusion, thereby making it difficult to find out the detail of evidence resulting in a conclusion. Therefore, as a novel tool for diagnosis and treatment, AI should be validated against current quality standards to ensure clinical effectiveness and safety in clinical practice. In this study, an independent database from our center was used to validate the performance of our models. It was demonstrated that convolutional neural networks could be used to assist in the classification and mutation prediction, based on histopathological H&E slides in liver cancer. However, the model still needs to be improved and validated by larger studies in the future. Even though it is impossible for AI to completely replace humans in practice nowadays, it is still a useful and effective tool to assist clinicians in dealing with repetitive work to provide important prognostic and therapeutic information. For example, mutation prediction could serve as a screening tool to improve cost-efficiency before immunohistochemistry or next-generation sequencing.

Overall, the study demonstrates that convolutional neural networks can predict histopathological grade and mutation in liver cancer. Although AI is likely to be a useful tool to assist surgeons and pathologists in classification of WSIs of HCC, the black box that how to get the conclusion is unclear and should be further studied. Besides, it is the first study to predict the gene mutation in HCC, meanwhile, internal and external validation cohorts were utilized to improve the accuracy of the model. In addition, the information on pathology and gene mutations may potentially be significant in applying the appropriate targeted therapy to HCC patients, thereby improving the performance of precision medicine.

The present study has several limitations to discuss. On the one hand, the size of the validation cohort is small. On the other hand, the model is not a complete replacement for pathologists’ examination, which included the diversity and heterogeneity of tissues that pathologists typically inspect (e.g., inflammation, necrosis, and blood vessels) and some clinical factors. Therefore, further validation of our model is necessary in a larger dataset with multiple centers and clinical factors or characteristics should be considered in further study. Moreover, EASY DL platform is exclusively available in Chinese which considerably limits the scope and audience targeted. To address the limitation, we provided the step-by-step instruction (figures and detailed English descriptions) for training deep-learning models via EASY DL, which was available at GitHub named “How_to_use_EASY_DL”.

In conclusion, our study demonstrated that the convolutional neural networks could assist pathologists in the classification of liver cancer and the detection of gene mutation. It also revealed that this method might be successfully adopted for other types of solid tumors.

METHODS

Prepare histopathological tiles dataset of liver cancer

The frozen slide images and the corresponding cancer information were obtained from the GDC-portal (https://portal.gdc.cancer.gov/). On slide-level, there were 491 WSIs (HCC vs. normal liver tissue, 402 vs. 89), 383 WSIs of HCC with available histopathological grade (well vs. moderate vs. poor, 55 vs. 187 vs. 141) and 387 WSIs of HCC with correspondence gene mutation information. Besides, 67 WSIs of HCC with completed information and 34 WSIs of normal liver tissue were selected from Sir Run-Run Shaw Hospital. All WSIs should be cropped into multiple small “tiles” at a magnification of 20X. The majority of slides could be cropped into more than 200 “tiles” on region (tiles)-level (Supplementary Fig. 1). Each tile was saved as a JPG format by nonoverlapping 256 x 256-pixel windows. In order to avoid heterogeneity, each tile, where less than 80% of the surface was covered by tissue, should be removed (Fig. 4). Finally, the liver cancer tiles dataset consisted of four subsets, including the training, testing, internal validation, and external validation sets. The data in the training and internal validation cohorts from the Genomic Data Commons portal (https://portal.gdc.cancer.gov/) were publicly available without restriction, authentication or authorization. The independent external validation cohort we used consisted of slide images without identifiable information and all...
participants had provided written informed consent. Our study was approved by the SRRSH of Medicine Institutional Review Board (KY20181209-5).

Technical detail on frozen slides in the external validation cohort

The obtained specimens (e.g., liver tissues) were macroscopically examined, measured, sectioned through their longest axis, and then midsections were examined. The material was frozen at \(-28^\circ\text{C}\), cut into 5–10 µm thick sections, Hematoxylin-Eosin (H&E) stained, and then analysed by pathologists with the light microscope. There were 67 out of 70 patients diagnosed as HCC and the related frozen slide were collected. Notably, normal liver tissues cannot be available in half of the obtained specimens, because normal liver tissues should be at least 2 cm away from tumors. Therefore, there were only 34 WSIs of normal liver tissues. In order to obtain digital pathology images, each

![Fig. 3](image_url)  
**Fig. 3** Prediction of the ten most common mutated genes in liver cancer using our deep-learning model and histopathology images.  
*a* comparison of the mutation and wild type in the distribution of the mutation probability in genes from tiles.  
*b* comparison of the mutation and wild type in the distribution of the mutation probability (Predicted $P>0.5$) in each slide. $P$ values were estimated with the two-tailed Mann–Whitney U-test ($**P\leq 0.01$; ***$P\leq 0.001$). For the two box plots, the middle line within the box represents the median; box limits represent 95% upper and lower quartiles; and whiskers represent the minima and maxima.

![Fig. 4](image_url)  
**Fig. 4** Strategy of preparing tiles dataset. First, each WSI of liver tissue was selected from GDC-portal or SRRSH. Then, they were cropped into lots of tiles. Finally, the tiles less than 80% area of surface with tissue were removed, and the remaining tiles were used for further analysis.

| Table 4. The performance of our models at mutation prediction in the external validation set. |
| Mutations | Per-tile AUC | Per-slide AUC after aggregation by Average predicted probability | Percentage of positive tiles |
|------------|-------------|-----------------------------|---------------------------|
| **CTNNB1** | 0.805 (0.759–0.851) | 0.898 (0.810–0.966) | 0.817 (0.713–0.922) |
| **FMN2**   | 0.727 (0.666–0.789) | 0.737 (0.613–0.861) | 0.838 (0.742–0.935) |
| **TP53**   | 0.736 (0.696–0.777) | 0.770 (0.650–0.890) | 0.715 (0.591–0.840) |
| **ZFX4**   | 0.720 (0.675–0.765) | 0.724 (0.591–0.858) | 0.751 (0.614–0.888) |

1. Each WSI from HCC patient  
2. Cropped into lots of tiles  
3. Remove tiles less than 80% area of surface with tissue
Deep-learning with convolution neural networks

Typical convolutional neural networks contain several levels of convolution filters, pooling layers, and fully connected layers. In our study, we primarily used inception V3 architecture, which makes use of inception modules which are made from a spread of convolutions having different kernel sizes and a max-pooling layer. The initial five convolution nodes are combined with two max-pooling operations and followed by 11 stacks of inception modules. A fully connected layer to the end of the inception modules was then added to permit us to utilize the pre-trained model and finetune the parameters for our own task. Finally, a softmax layer was added as a classifier outputting a probability for every class, and the one with the highest probability was chosen as the predicted class.

We used the pre-trained model offered by TensorFlow and finetuned it using histopathological images. It was pre-trained on the ImageNet dataset and available at the Tensorflow-Slim image classification library (http://tensorflow.org). We initialized the parameters from the pre-trained model because pre-training can speed up the convergence of the network. Most importantly, it was difficult to train a deep network with a small number of images due to the massive number of network parameters.

Comparison with pathologists

One hundred and one WSIs of liver tissues without a label from the external validation cohort were used to test pathologist’s performance and compared with our model performance. All pathologists should report whether there is HCC, and if there is HCC, they should report histopathological grade via our model performance. All pathologists should report whether there is HCC, and if there is HCC, they should report histopathological grade via the R 3.6.0 (https://www.r-project.org). Finally, the ten most significant prognosis-related gene mutations, including ARID1A, ASH1L, CSMD1, CTNNB1, EYS, FEN2, MDM4, RB1, TP53, and ZFX4 were identified (Fig. 5).

Training deep-learning network

Pathological diagnosis was the primary endpoint of interest for the classifier that recognizes tumors from normal liver tissue and the assessment of the histopathological grade. The status of gene mutation (mutation or wild type), based on the next-generation sequencing results, was the primary prerequisite in the classifier of mutation prediction. The model’s training strategy was based on an easy-to-use platform called EASY DL (https://ai.baidu.com/easydl/) that uses PaddlePaddle deep learning framework V3.0 created by Baidu Brain AI technology, inception V3 network developed by Google, and packaging code form Coudray and co-workers. The training set was used for training, and the testing set was used to evaluate the performances, finetune those parameters, and improve the models. A final model was selected according to the results of the testing set, where the F1-scores as a stopping rule. Notably, the subsets were grouped based on HCC patients rather than the WSIs. This method could maximize the size of the training set and avoid training and testing on tiles originating from the same human subjects. Thereby preventing the classifier from relying on intra-subject correlations between samples and resulting in inflated estimates of accuracy. In order to reduce selection bias, the performance of our model was then validated in the internal and external validation sets.

Statistical analysis

The ten most common and prognostic mutated genes were identified using the LASSO Cox regression model, and any differences of overall survival were evaluated by the Kaplan–Meier method with a log-rank test. The performance of those models was evaluated with F1-scores, MCC, and AUC. The F1-scores, ranging from 1 (perfect) to 0 (bad), is the harmonic average of the precision and recall21. MCC ranges from 1 (perfect) to –1 (bad). In addition, the probability of gene mutation was estimated and compared using the two-tailed Mann–Whitney U-tests. A P value of less than 0.05, was considered as statistical significance.

DATA AVAILABILITY

The slide images and the corresponding cancer information were uploaded from the Genomic Data Commons portal (https://portal.gdc.cancer.gov/) and were in whole or in part based upon data generated by the TCGA Research Network (http://cancergenome.nih.gov/). These data were publicly available without restriction, authentication, or authorization. The datasets for the independent cohorts generated and/or analyzed during the current study are available from the corresponding author (X.J.C.) upon reasonable request and through collaborative investigations.
CODE AVAILABILITY

The codes that were used to train and validate the deep-learning model in the manuscript are available at https://github.com/drmachen-gbc/HCC-deep-learning. It also used other open-source codes (inception V3), which were available at https://github.com/openslide/openslide-python.

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AUTHOR CONTRIBUTIONS

M.Y.C., J.S.C., W.T., H.Y., and B.Z. were involved in the study design, data collection and analysis, and drafted the paper; H.P.Z., S.J., and Q.J.M. collected and checked data; M. Y., C.V., X.C., and W.T. were involved in the study design, data collection and analysis, and drafted the paper; H.P.Z., S.J., and Q.J.M. collected and checked data; M. Y., C.V., X.C., and W.T. revised the paper; X.J.C. designed, supervised the study; and all authors wrote the paper.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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Correspondence and requests for materials should be addressed to H.Y. or X.C.

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