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Artificial Intelligence-Driven LRRC15 Expression and Clinicopathological Prediction in Colorectal Carcinoma Using Weakly Supervised Learning

Authors: *Jongwon Lee[1,2], Sungyong Jang[3], Ming Fan[3], Donghyeok Jo[2], Yeon-Wook Kim[4], Young Joo Yang[5,6], Deok-beom Jung[7,8], Dong-Joo Kim[2], Seung-Jae Myung[7,9,10], Baek-Hui Kim[1], Seung-Mo Hong[7,11,*]*

Affiliations: *[1]Department of Pathology, Korea University Guro Hospital, Seoul, Republic of Korea [2]Department of Brain and Cognitive Engineering, Korea University, Seoul, Republic of Korea [3]AIVIS corp., Seoul, Republic of Korea [4]Asan Institute for Life Sciences, Asan Medical Center, Seoul, Republic of Korea [5]Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, Korea [6]Institute for Liver and Digestive Diseases, Hallym University, Chuncheon, Korea [7]Digestive Diseases Research Center, University of Ulsan College of Medicine, Seoul, Republic of Korea [8]Department of Medicine, University of Ulsan College of Medicine, Seoul, Republic of Korea [9]Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea [10]Edis Biotech, Songpa-gu, Seoul, Republic of Korea [11]Department of Pathology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea*

**Corresponding author*

Jongwon Lee,. alyssa8921@gmail.com,
Seung-Mo Hong, smhong28@gmail.com

INTRODUCTION

- **Background**: LRRC15 (Leucine-rich repeat-containing 15) is expressed in cancer-associated fibroblasts (CAFs) and correlates with poor prognosis in various cancers. While immunohistochemical (IHC) staining enables in-situ evaluation, LRRC15 IHC is uncommon and its quantification subjective.
- **Objective**: To address these limitations, we developed an AI system to: **1) automate LRRC15 quantification in IHC using YOLOv8, and 2) predict LRRC15 IHC expression and clinicopathologic factors from hematoxylin and eosin (HE) images using multiple instance learning (MIL)**.

METHODS

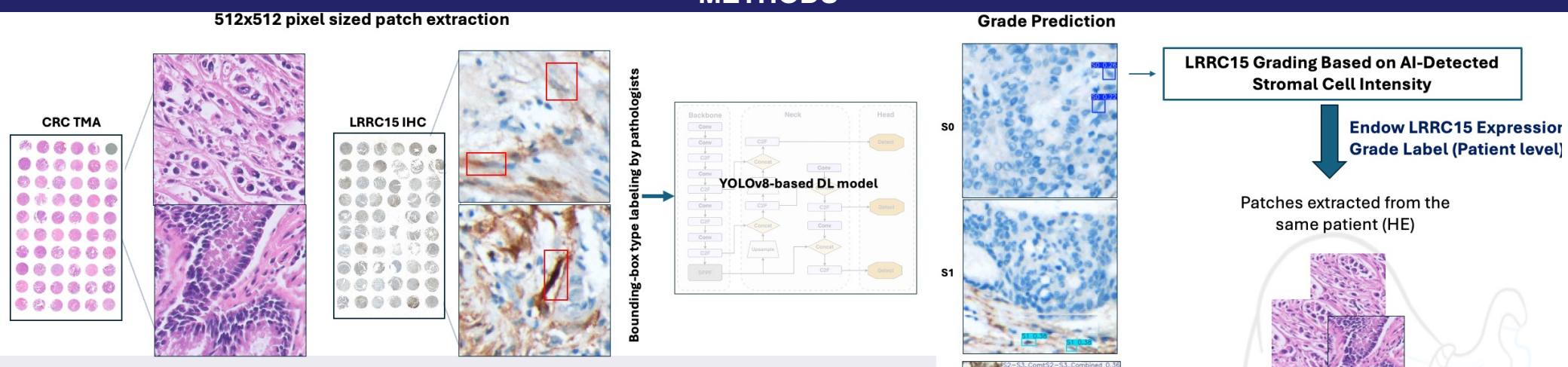


Figure 1. Artificial Intelligence Based LRRC15 IHC Grading Schema. Training for LRRC15 grade detection model utilized the patches from AMC dataset. 2,624 patches with 50 patches receiving detailed bounding box annotations where individual cells were marked and assigned staining intensities ranging from 0 to 3. For the YOLOv8 model development, we implement a three-tier classification system, categorizing LRRC15 expression as S0 for negative, S1 for low expression, and S2-3 for moderate to high expression combined. Subsequently, we develop a multiple instance learning model with attention mechanisms to predict LRRC15 grades directly from H&E-stained images from 124 patients combining both hospitals' data.

- As an initial step, we developed an **LRRC15 CAF grading detection model** using 113 patients (59 CRC, 54 normal) from AMC for training and 74 CRC patients from KUGH for validation. The model was trained for 150 epochs, completing in 1.12 hours.
- We evaluated **6 MIL architectural variants** using ResNet34 backbone on 124 colorectal cancer patients. Key variations tested included: attention-based versus mean pooling aggregation, learnable versus fixed thresholds, binary versus multi-class (3-class, 4-class) classification, and different patch counts (8-20 per patient). Models processed 384×384 pixel patches (except high-resolution variant at 512×512). Training used 3-fold cross-validation with 60-20-20 train-validation-test split.

RESULTS

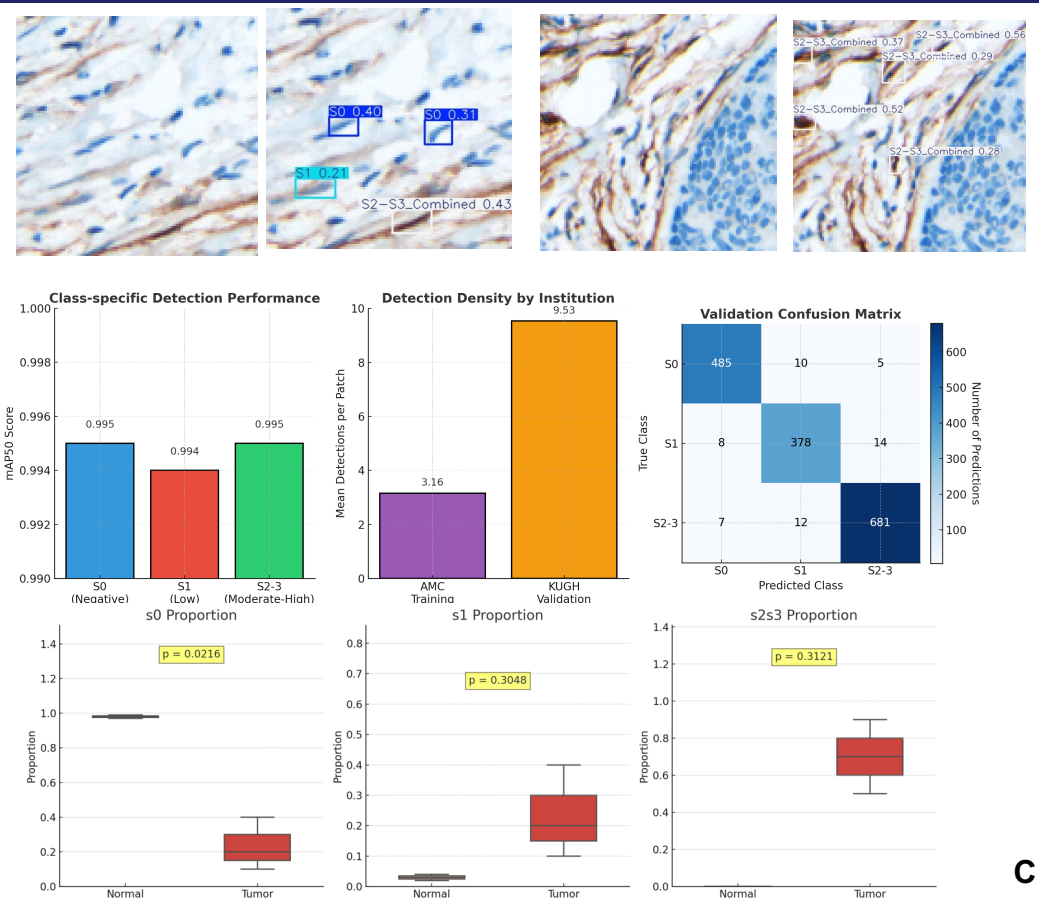
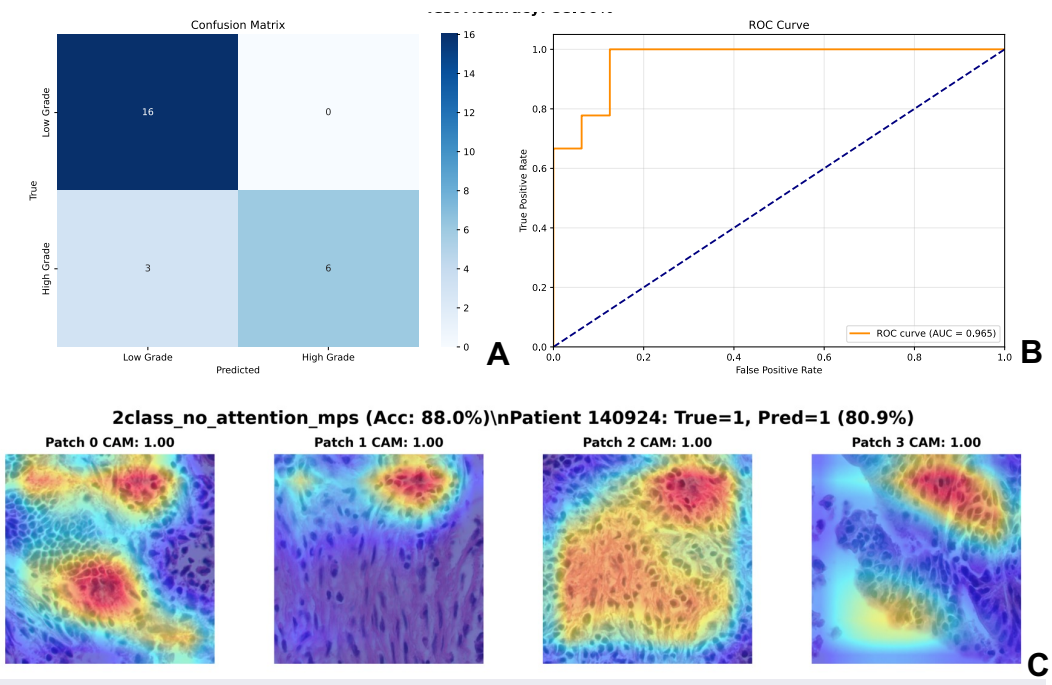


Figure 2. LRRC15 IHC Grading Model Performance. (**A**)Representative LRRC15 IHC staining examples show YOLOv8 detection of S0 (negative, blue boxes), S1 (low expression, cyan boxes), and S2-3 (moderate-high expression, white boxes) in CAFs. (**B**) Class-specific mAP50 scores exceed 0.994 for all categories, Detection density analysis reveals 3-fold higher LRRC15-positive cell identification in KUGH validation cohort (9.53 per patch) compared to AMC training cohort (3.16 per patch), suggesting institutional variations in tissue characteristics or patient populations. The validation confusion **matrix confirms excellent classification accuracy with diagonal dominance and minimal misclassification between expression categories.** (**C**) Box plots display significant **differences in LRRC15 expression proportions between normal and tumor tissues** across all classification tiers ($p < 0.05$), with S2-3 proportions increasing from 0.2% in normal to 60.8% in tumor tissue.



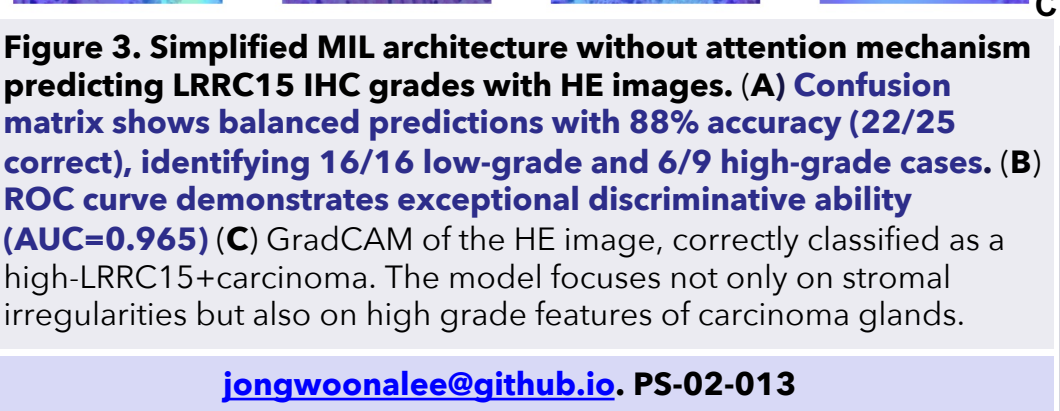


Figure 3. Simplified MIL architecture without attention mechanism predicting LRRC15 IHC grades with HE images. (**A**) **Confusion matrix shows balanced predictions with 88% accuracy (22/25 correct), identifying 16/16 low-grade and 6/9 high-grade cases.** (**B**) **ROC curve demonstrates exceptional discriminative ability (AUC=0.965)** (**C**) GradCAM of the HE image, correctly classified as a high-LRRC15+carcinoma. The model focuses not only on stromal irregularities but also on high grade features of carcinoma glands.

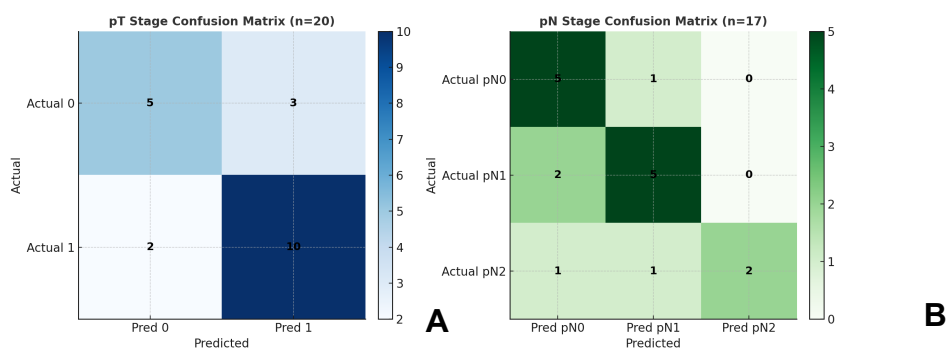


Figure 4. MIL model performance for pathological stage prediction from H&E images. (**A**) For pT stage prediction (n=20), the model achieved 75% overall accuracy with balanced accuracy of 72.9%, showing better **performance for muscle-invasive tumors (pT2+: 83.3%, 10/12 correct)** compared to non-invasive cases (pT1-: 62.5%, 5/8 correct). (**B**) For pN stage prediction (n=17), **overall accuracy reached 70.6%, with highest performance for node-negative cases (pN0: 83.3%, 5/6 correct)**

Summary:

1) LRRC15 Grading AI Model Performance: Achieved exceptional LRRC15 detection accuracy with robust performance across all expression categories using an efficient and fast YOLOv8 based model

2) H&E Prediction of LRRC15: MIL model showed substantial predictive capability of LRRC15 using only HE patches.

3) Clinical Implications: Automated LRRC15 IHC quantification ready for clinical implementation; H&E screening could potentially reduce unnecessary staining in LRRC15 IHC cases and even stage evaluation

jongwoonalee@github.io. PS-02-013