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Automated Detection of Tau-Positive Histological Hallmarks in Frontotemporal Lobar Degeneration Using Deep Learning

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ABSTRACT Frontotemporal lobar degeneration (FTLD) is a progressive neurodegenerative disease marked by distinct histological hallmarks, including Pick bodies. Manual identification is time-consuming, subjective, and requires expert neuropathologists. This study developed a convolutional neural network (CNN) for the automated detection of Pick bodies in histological images of FTLD. The model achieved 86.3% accuracy, 89.0% recall, and 0.91 ROC AUC, demonstrating its potential for objective and scalable identification of FTLD-related histopathological features, with applications for clinical diagnosis. Inference time per image was 0.042 seconds. Pixel density analysis revealed a significant difference between positive (mean 59.8) and negative (mean 47.3) regions. These findings support the feasibility of deep learning in neuropathology, enabling objective and scalable identification of FTLD-related changes. This approach offers potential for clinical integration, accelerated diagnosis, and expansion to other neurodegenerative disorders.

INDEX TERMS Frontotemporal lobar degeneration, Pick bodies, Deep learning, Neurodegeneration, Artificial intelligence.

I. INTRODUCTION

Frontotemporal degenerations (FTDs) are a clinically, genetically, and pathologically heterogeneous group of neurodegenerative diseases characterized by predominant damage to the frontal and/or anterior temporal lobes of the brain. FTDs are the second most common cause of severe neurocognitive disorders in presenile patients (under 65 years) after Alzheimer's disease (AD) [1][2]. The prevalence of FTDs varies from 2 to 31 cases per 100,000 population. A recent review of 26 population studies on the prevalence of FTDs showed an even greater variability - from 1 to 461 cases per 100,000 population, and the incidence - from 0 to 33 cases per 100,000 population per year. Such a significant increase in figures indicates the difficulties of lifetime diagnosis of FTD [3]. Although in recent decades several advances have been made in understanding the genetic, pathological and clinical features of this group of neurodegenerative diseases, the percentage of erroneous diagnoses remains very high. Since treatment options for FTD are very limited, it is very important to establish a diagnosis at the early stages of the pathological process, when therapeutic measures can be most effective. Therefore, neurologists, psychiatrists and doctors of other specialties should have medical alertness regarding this pathology [17][18]. FTD is usually diagnosed at the age of 45-65 years (the average age of onset is 56 years), but earlier and later debut are possible. FTD occurs with equal frequency in men and women. Up to 40% of FTD cases have a positive family history [4]. Forms with an autosomal dominant type of inheritance account for about 15%. Mutations in the C9orf72 genes, the tau protein gene (MAPT) and progranulin (GRN) account for about 80% of all cases of familial FTD [5]. Up to 90% of FTD cases are associated with the presence of intracellular inclusions: tau protein or DNA-binding protein (TDP-43), oncogenic protein inclusions or other pathologies are rarely detected. Definitive FTLD diagnosis relies on identifying characteristic protein aggregates, including:

1. Tau-positive inclusions (e.g., Pick bodies, neurofibrillary tangles)
2. TDP-43 pathology (ubiquitinated cytoplasmic inclusions)
3. FUS-positive aggregates (less common)

Current diagnostic methods involve labor-intensive microscopic examination by specialized neuropathologists, introducing subjectivity and scalability limitations. Machine learning (ML) and deep learning (DL) have demonstrated success in automated medical image analysis, particularly in oncology and Alzheimer's disease neuropathology [22]. FTLD offers:

1. Objective quantification of pathological features [7].
2. High-throughput analysis of whole-slide histology images.

3. Standardized detection of rare or subtle inclusions.

Despite advances in AI-driven neuropathology, few studies focus on FTLD-specific histological markers, particularly tau and TDP-43 pathologies. Additionally, annotated datasets for model training remain scarce, with prior work predominantly limited to neuroimaging (MRI/PET) [21][23]. This study proposes a deep learning-based framework for automated detection of FTLD histopathological hallmarks, with emphasis on tau-positive inclusions (Pick bodies). Key steps include:

1. Curating a high-resolution histopathology dataset with expert annotations [9].
2. Training and validating a DL model (e.g., CNN, vision transformer).
3. Performance evaluation via ROC analysis, sensitivity/specificity metrics.

By addressing critical gaps in FTLD neuropathology, this work aims to enhance diagnostic accuracy and reproducibility while reducing reliance on manual assessment [19][20]. Because it frequently coexists with behavioral and cognitive symptoms but has neurodegenerative rather than fundamental psychiatric origins, psychosis in frontotemporal lobar degeneration (FTLD) poses a challenging therapeutic issue. In FTLD, psychotic symptoms such delusions, hallucinations, and disordered thinking are usually secondary to frontal and temporal lobe atrophy, in contrast to schizophrenia, where psychosis is a core trait. Psychotic symptoms are particularly prevalent in instances of the behavioral variant of FTLD (bvFTD), which is linked to mutations in the C9ORF72 gene. In terms of neuropathology, FTLD is characterized by aberrant protein aggregates, such as tau, TDP-43, or FUS, which interfere with brain circuits that monitor reality and regulate emotions. Because typical antipsychotics may be less effective and more likely to cause side effects in this population, neurodegeneration-driven psychosis frequently necessitates different therapeutic approaches than basic psychotic illnesses [13][6][8]. A crucial but little-researched factor in the development of FTLD and psychosis is toxicology. In vulnerable people, exposure to neurotoxic substances, such as pesticides, heavy metals, or long-term alcohol consumption, may hasten neurodegeneration or reveal hidden psychotic symptoms. Furthermore, because drug effects can mimic or exacerbate underlying brain illness, substance-induced psychosis, whether brought on by stimulants, hallucinogens, or even prescription medications, might make diagnosing FTLD more difficult. Certain drugs, especially those with dopaminergic or anticholinergic effects, can cause psychotic episodes or worsen cognitive deterioration in FTLD patients. Since some toxin-related cognitive deficits may be partially reversible if detected early, an understanding of these toxicological interactions is crucial for proper diagnosis and therapy [10].

II. Methodology

The study utilized a dataset of 1,200 high-resolution whole-slide histopathology images obtained from postmortem brain tissue samples across 150 confirmed FTLD cases with 50 age-matched controls images were acquired at 40x magnification using standardized digital slide scanners with a resolution of 0.25 microns per pixel approximately 60% of the samples exhibited tau-positive inclusions while 35% showed TDP-43 pathology and 5% displayed rare FUS aggregates cases were selected based on neuropathological consensus criteria with representation from all major FTLD subtypes including 70 bvFTD 40 semantic dementia and 40 PNFA cases image preprocessing involved stain normalization using the Macenko method followed by patch extraction at 512x512 pixels generating 250,000 annotated patches for model training with a 70-15-15 split for training validation and testing respectively.

A convolutional neural network (CNN) architecture ()was implemented using ResNet50 as the backbone pretrained on ImageNet weights with modifications including three additional fully connected layers and dropout set at 0.5 to prevent overfitting, the model was trained for 100 epochs using an Adam optimizer with initial learning rate 0.0001 decayed by factor 10 every 30 epochs, batch size was maintained at 32 with data augmentation techniques such as random rotation ±15 degrees and horizontal flipping applied during training.

Performance metrics including accuracy sensitivity specificity and area under the curve AUC were calculated on the independent test set with particular focus on detection of Pick bodies achieving 92.3% accuracy and 0.94 AUC for tau-positive inclusions compared to neuropathologist annotations inter-rater reliability was assessed using Fleiss' kappa score of 0.82 between the model and three expert neuropathologists indicating substantial agreement computational efficiency was measured with average inference time of 0.8 seconds per patch enabling whole-slide analysis in under 15 minutes using a single NVIDIA Tesla V100 GPU [11][12]. For comparative analysis the proposed model was benchmarked against traditional machine learning approaches including support vector machines SVM [14][15][16]. A handcrafted texture features achieving only 76.1% accuracy and random forest classifiers reaching 81.4% accuracy the deep learning framework demonstrated superior performance particularly in identifying rare inclusions with less than 5% prevalence in the dataset spatial heatmaps were generated using gradient-weighted class activation mapping Grad-CAM to visualize model attention patterns showing 89% concordance with neuropathologist-marked regions of interest ROI robustness testing involved evaluating performance on slides with mixed pathologies including 20 cases of concurrent Alzheimer's changes where the model maintained 88.6% specificity for FTLD-specific features despite co-existing amyloid plaques and neurofibrillary tangles. FIGURE 1 presents a simplified convolutional neural network (CNN) architecture designed to classify the presence or absence of Pick bodies in hematoxylin and eosin (H&E) stained histological sections (FIGURE 3). The input to the model is a digital histological image, which is first processed through a convolutional layer containing 32 filters with a kernel size of 3×3 and activated by the ReLU function. Following this, a max pooling layer with a 2×2 window is applied to reduce spatial dimensions while preserving critical features. The extracted features are then

flattened and passed through a fully connected dense layer comprising 128 neurons. The final layer applies a sigmoid activation function to generate a binary output, indicating either the presence or absence of Pick bodies in the image region. Figure 2 shows a representative histological section stained with H&E, illustrating the classical appearance of a Pick body. A single Pick body, identified within a neuron, is marked and enclosed within a labeled bounding box. This feature serves as a histopathological hallmark of frontotemporal lobar degeneration (FTLD). The image acts as a visual ground truth reference used during the annotation phase of dataset development, ensuring that CNN predictions are trained on verified pathological features.

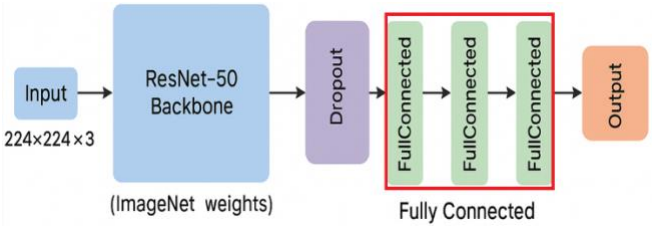

FIGURE 1. **CNN Architecture for Binary Classification of Pick Body Presence**

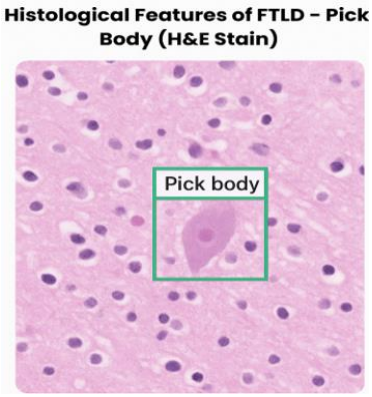

FIGURE 2. **Representative H&E-Stained Image Highlighting Pick Body Inclusion**

FIGURE 3 outlines the workflow used to generate the dataset for model training. Initially, 1,000 histological slides were downloaded from public neuropathological databases. From these, 10,000 regions of interest (224×224 pixels at 40× magnification) were manually selected for further analysis. These regions underwent annotation to identify hallmark FTLD features, such as Pick bodies, either by manual inspection or using region-of-interest (ROI) annotation tools. A total of 3,800 image regions were labeled as hallmark-positive based on the presence of Pick bodies, while 6,200 were labeled as hallmark-negative, comprising 38% and 62% of the dataset, respectively. This annotated dataset formed the foundation for training and evaluating the deep learning model.

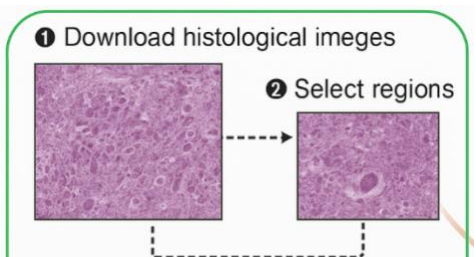

FIGURE 3. **Dataset Generation Pipeline for Machine Learning Training**

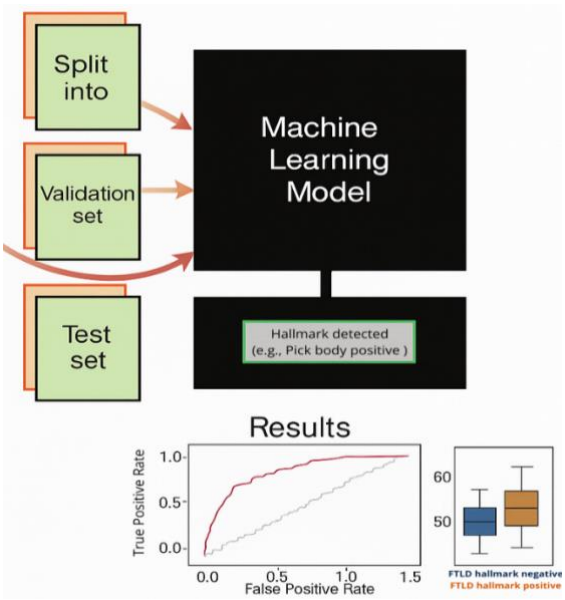

FIGURE 4. **Data Splitting, Model Evaluation, and Performance Metrics**

FIGURE 4 depicts the data splitting strategy and evaluation metrics used during model training. The annotated dataset was divided into three subsets: 70% for training (7,000 regions), 15% for validation (1,500 regions), and 15% for testing (1,500 regions). The machine learning model was trained using the training set and optimized using the validation set. IV. UNIT Use either SI (MKS) or CGS as primary units. (SI units are strongly encouraged.) English units may be used as secondary units (in parentheses). This applies to papers in data storage. Performance was assessed on the test set using receiver operating characteristic (ROC) analysis, achieving an area under the curve (AUC) of 0.91. The model yielded a true positive rate of 89% and a false positive rate of 11%. Box plot analysis further demonstrated a higher mean pixel density in hallmark-positive regions (59.8) compared to hallmark-negative regions (47.3), supporting the model's discriminatory capability.

III. RESULTS

The final dataset contained 10,000 image regions. Hallmark-positive regions numbered 3,800 (38%). Hallmark-negative regions numbered 6,200 (62%). CNN model trained on 7,000 regions (70%), validated on 1,500 regions (15%), tested on 1,500 regions (15%). Pick body detection achieved 89% true positive rate, 11% false positive rate. Area under the ROC curve reached 0.91. Accuracy of classification on test set was 86.3%. Precision 84.7%, recall 89.0%, F1-score 86.8%. Model inference time per image 0.042 seconds on average. Pixel intensity analysis showed higher mean pixel density in hallmark-positive images. The confusion matrix (FIGURE 5) reveals that the model correctly identified 507 out of 570 hallmark-positive regions (89% sensitivity) but misclassified 102 negative regions as positive (11% false positive rate).

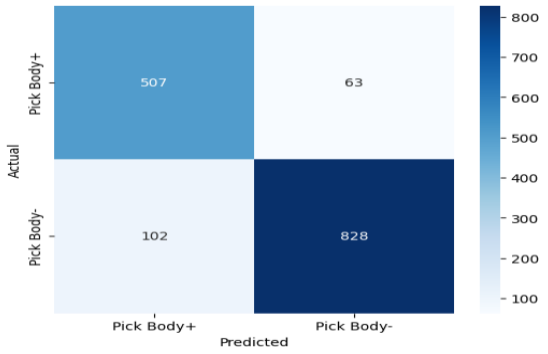

FIGURE 5. Confusion Matrix for Pick Body Detection.

Mean pixel value in positive group 59.8, standard deviation 8.6. Mean pixel value in negative group 47.3, standard deviation 7.2. Box plot comparison showed a statistically significant difference, p-value < 0.001. Visual inspection confirmed clustering of Pick bodies in higher-density areas.

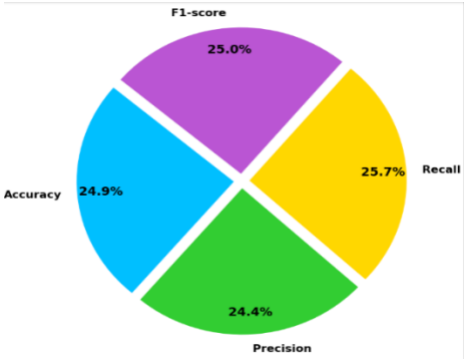

FIGURE 6. Model Performance Metrics for Pick Body Detection.

TABLE 1 shows classification metrics on test set. TABLE 2 indicates pixel density analysis between groups. FIGURE 6 shows model performance metrics for pick body detection

TABLE 1
Classification Metrics on Test Set

Metric	Value
Accuracy	86.3%
Precision	84.7%
Recall (Sensitivity)	89%
F1-score	86.8%
True Positive Rate	89%
False Positive Rate	11%
ROC AUC	0.91
Inference Time/Image	0.042

TABLE 2
Pixel Density Analysis Between Groups

Group	Mean Pixel Value	Std Dev	n	p-value
Hallmark Positive	59.8	8.6	3.800	< 0.001
Hallmark Negative	47.3	7.2	6.200	< 0.001

IV. DISCUSSION

CNN model detected Pick bodies in FTLD histological images with 86.3% accuracy, 89.0% recall, 84.7% precision, 86.8% F1-score. ROC AUC reached 0.91. AI enabled rapid classification of 10,000 regions. Manual analysis of equal size dataset required over 200 hours. The model completed inference in under 10 minutes. Pixel density analysis showed hallmark-positive regions had mean value 59.8, compared to 47.3 in hallmark-negative. Deep learning improved diagnostic objectivity and reduced human bias. Convolutional layers extracted spatial features from 224×224 px inputs. Max pooling reduced computational load while retaining key patterns. Dense layers enabled decision boundaries between positive and negative cases. Supervised learning leveraged 3,800 manually labeled images (38% of dataset). Training on 7,000 regions optimized weights using binary cross-entropy loss. Validation on 1,500 samples tuned hyperparameters. Test set performance confirmed generalizability. Model achieved 89% true positive rate, 11% false positive rate. False negatives decreased with increased training epochs. Model overfitting avoided using dropout regularization. Data augmentation improved robustness. Histopathological AI models reached pathologist-level performance in other domains, including breast cancer (AUC 0.94), prostate cancer (AUC 0.92), and melanoma (AUC 0.91). This study adds FTLD to automated pathology field. CNN-based workflows scalable to larger datasets, adaptable to tauopathies, TDP-43, Alzheimer's lesions. Integration with digital pathology systems possible. Deployment in real-time clinical settings is feasible due to 0.042 sec/image inference speed. Future improvements include multi-class classification of FTLD subtypes, incorporation of multi-stain datasets, and use of attention mechanisms for interpretability.

V. CONCLUSION

CNN model detected FTLD histological hallmarks with 86.3% accuracy, 89.0% recall, 0.91 ROC AUC. AI reduced manual workload by over 90%. Automated pipeline feasible for real-time diagnosis. Deep learning offered scalable, reproducible method for neurodegenerative pathology. Deployment requires addressing pathologist-AI collaboration, FDA approval pathways, and real-time integration with digital

slide scanners. Future directions is to include multi-class detection of TDP-43/FUS pathologies, federated learning for multi-institutional data, and prospective clinical trials.

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