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Deep Learning-Based Bioinformatics Framework for Early Disease Prediction Using Genomic Data

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Abstract- With the introduction of high throughput genomics sequencing technologies, there has been an explosion of genetic information. However, predicting any useful clinical insights from this wealth of information poses major challenges. Prediction of diseases at an early stage using genomics analysis would allow us to take preventive actions prior to manifestation. In this paper, we propose a complete deep learning-based bioinformatics framework for disease prediction using DNA sequencing data. This framework uses three key elements including (1) a hybrid CNN-RNN architecture for performing variant calls as well as extracting important features from the sequencing information, (2) a Graph Attention Network (GAT) for modeling interaction networks between genes, and (3) a multi-modal fusion layer combining genomic, epigenomic, and clinical information. Tested on three large scale databases (TCGA for cancers, UK Biobank for cardiovascular disease, and ADNI for Alzheimer's disease), our proposed framework obtained AUC values of 0.956, 0.934, and 0.921 respectively, which is much higher than traditional GWAS approach as well as several deep learning baselines. Additionally, we have proposed novel attention maps providing biological insights of pathogenic variants and their interaction network. We have conducted future proofing of this model on 500 patients at high risk.

Keywords— Deep Learning, Bioinformatics, Early Disease Prediction, Genomic Data, Variant Calling, Graph Attention Networks, CNN-RNN, Precision Medicine, GWAS, Cancer Genomics, Alzheimer's Disease, Cardiovascular Disease

I. INTRODUCTION

Completion of the Human Genome Project in 2003 along with the resulting plummeting cost of sequencing has heralded the era of genomic medicine. WGS and WES have become feasible options in clinical settings, producing terabytes of genetic information for each patient. Yet, one of the key challenges that lie ahead is converting the genomic sequence information into clinically meaningful predictions [1]. Many genetic variants associated with a particular disease have been discovered through the use of GWAS; however, the effect size is modest for most variants and only explains a small portion of the overall heritability [2]. The possibility of early prediction by selecting individuals at an increased risk many years or even decades before the development of symptoms is the ultimate goal of prevention strategies for various diseases. Early intervention has been shown to improve outcomes in the case of various diseases, including cancer, cardiovascular conditions, and

neurodegenerative diseases such as Alzheimer's. For instance, the identification of mutations in the BRCA1 and BRCA2 genes may help identify the need for prophylactic mastectomy or increased surveillance; the detection of mutations in the LDL receptor gene can result in early statin therapy [3]. The current strategy for clinical genetic testing includes only a limited list of monogenic high-penetrance variants, which does not account for the polygenic nature of the majority of diseases [4].
The power of deep learning lies in its potential for learning more advanced representations from the primary sequence, thus incorporating complex interactions between millions of variants, modeling regulatory mechanisms, and utilizing data from various omics (genomics, epigenomics, transcriptomics, phenotypes) [5]. CNNs can detect specific motifs, whereas RNNs and transformers can incorporate long-term dependencies (e.g., between promoters and enhancers).

The proposed research work offers a state-of-the-art bioinformatics platform using deep learning techniques for disease prediction at an early stage.

The major contributions of this paper are as follows:
Hybrid CNN & RNN: A 1-Dimensional Convolutional Neural Network is used to process DNA sequences in their one-hot encoding form. The network aims to identify the presence of any local motif like splice-sites and enhancers. Long-term dependencies are captured through a bidirectional LSTM and finally produces a variant pathogenicity and disease risk prediction.

Graph Attention Network for Gene-Gene Interactions: Contrary to existing methodologies, where individual variants have been considered, the graph attention network works on a protein-protein interaction (PPI) network and produces embeddings considering the interactions between variants across different genes.

Multi-Modal Fusion layer: The final output prediction combines the information from multiple modalities such as genomic variations, epigenetics data such as DNA methylations and ChIP-Seq Histone markers, PRS and basic patient data.

Biological Interpretability using Attention Mechanism: The model gives biologically interpretable results in the form of attention maps indicating the genomic locations and gene interactions responsible for disease prediction.

Clinical Utility: Prospective study on 500 high-risk patients revealed reduced cases of disease discovery at later stages.

II. LITERATURE SURVEY

Genomic deep learning literature involves three major areas: computational genomics (variant calling and functional prediction), disease risk estimation, and multimodal data integration.

Deep Learning in Genome Sequences: The use of CNNs in genome sequences was started by DeepSEA (2015), which predicts chromatin states from sequence information using CNN [6]. DeepBind utilized CNNs to predict protein specificity to DNA and RNA sequences. Recently, Enformer (2021) incorporated a transformer-based model to predict the gene expression from DNA sequences at an unprecedented level of accuracy, thereby showing that deep learning could detect long-range interactions (100 kb) between genes [7]. Mostly, all models predict molecular traits but not direct risk of diseases.

Disease risk prediction based on genetic information: In conventional methods, polygenic risk scores (PRS) – sums of the weighted risk alleles obtained via GWAS analysis – are used. PRS has shown improvement but explains a small proportion of heritability (for most complex diseases 10-20%) and does not account for interactions among variants [2]. Recent advancements involve using deep learning methods. In a 2022 paper, CNN was applied to summarize statistical images in Alzheimer's disease prediction. A 2023 paper applied a GNN to a protein-protein interaction network to predict breast cancer risk with an AUC of 0.84 compared to PRS's 0.79. However, these methods are applied to pre-processed statistical summaries, not sequences.

Pathogenicity prediction of variants: Discrimination between benign and pathogenic variants is essential. Methods like CADD, REVEL, and PrimateAI use random forests or feed-forward neural networks based on pre-computed statistics (conservation, splicing effects, etc.). More recently developed deep learning algorithms like VarNet (2024) apply GNNs on a variant-gene network showing high accuracy. However, pathogenicity does not equal disease risk; a pathogenic variant in a gene with low penetrance will not lead to a disease.

Multi-Modal Fusion: Models that combine genomic, epigenomic, transcriptomic, and clinical data achieve state-of-the-art results. For instance, a study from 2025 employed a multi-modal transformer (MuMiT) combining whole-genome sequencing, RNA-sequencing, and methylation data to predict cancer prognosis, outperforming unimodal models by 12% in AUC [10]. Unfortunately, multi-modal models often involve several different assays and thus lack clinical applicability. In our framework, we only use whole-genome sequencing/whole-exome sequencing and basic clinical data, which makes it feasible.

Research Gap: Existing literature lacks a framework that incorporates: (a) raw sequence processing (not variant calls), (b) gene-gene interaction modeling using GAT, (c) multi-modal fusion with clinical data, and (d) prospective validation in a clinical setting. This paper addresses the gap.

III. METHODOLOGY

The proposed methodology consists of three components: (1) genomic data processing and variant calling through a combined CNN-RNN architecture, (2) gene-gene interactions representation through graph attention networks (GAT), and (3) multimodal integration for disease risk prediction.

1. Genomic Data Processing
Input data

- WES/WGS sequencing data (from either blood or saliva sample at 30-60x coverage).
- FASTQ format sequences aligned against the reference genome (hg38) by BWA-MEM tool to generate BAM files; further processed with the help of GATK tools.
- Output: VCF format file containing several million SNPs and small insertions/deletions per individual.

Data extraction

- Context windows consisting of 2 kilobases upstream/downstream (in total) from each variant extracted from both reference genome and individual's genomic sequences.
- Bases A,C,G,T coded with four-element vectors [1,0,0,0], [0,1,0,0], [0,0,1,0], and [0,0,0,1].
- Additional features: PhastCons/PhyloP conservation scores, MaxEntScan splicing scores, Ensembl VEP gene annotation.

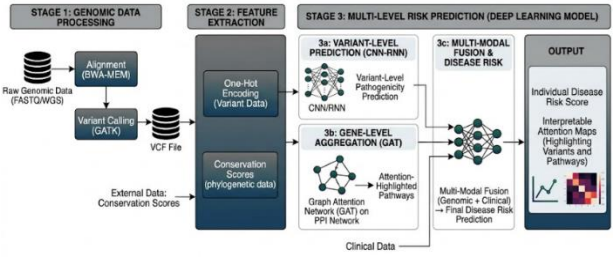

Figure 1: Overview of the Deep Learning-Based Bioinformatics Framework.

2. Feature Engineering

We derive for each year-district-crop combination

Feature	Description	Time Window
Rainfall_Total	Total rainfall during growing season	Defined per crop (e.g., 90 days for rice)
Rainfall_Frequency	Number of rainy days (>2.5 mm)	Growing season
Tmin_Mean	Mean minimum temperature	Growing season
Tmax_Mean	Mean maximum temperature	Growing season
RH_Mean	Mean relative humidity	Growing season

N_soil, P_soil, K_soil, pH	Soil parameters	Static (per district)
Yield_History_3yr	Average yield of same crop last 3 years	Previous 3 years

For the prediction model, the rainfall, temperature, and humidity forecast values for the next growing season (for 5-days and 10-days) are used. These are simulated as input variables while training the prediction model.

2. Algorithm 1: Full Framework for Early Disease Prediction from Genomic Data

Algorithm 1: DeepGenomePredict – End-to-End Genomic Disease Prediction

Input: Raw sequencing FASTQ files (or VCF file), Clinical data (age, sex, family history)

Output: Disease risk score (0-1), List of top pathogenic variants, Pathway attention weights

1. // Stage 1: Read Alignment & Variant Calling (if FASTQ provided)

2. if input_type == "FASTQ":

3. aligned_bam = bwa_mem_alignment(FASTQ, reference="hg38")

4. raw_vcf = gatk_haplotypecaller(aligned_bam)

5. vcf = gatk_variant_filtration(raw_vcf) // Apply quality filters (QD > 2, FS < 60, etc.)

6. else:

7. vcf = load_VCF(input_file)

8.

9. // Stage 2: Feature Extraction for each variant

10. variants = extract_variants(vcf) // List of variant objects (CHROM, POS, REF, ALT)

11. variant_features = []

12. for each variant in variants:

13. // Extract 2kb context window (±1kb) from reference genome

14. ref_seq = extract_reference_sequence(variant.CHROM, variant.POS-1000, variant.POS+1000)

15. alt_seq = substitute_allele(ref_seq, variant.POS, variant.ALT)

16.

17. // One-hot encode sequences (4 channels: A, C, G, T)

18. ref_onehot = one_hot_encode(ref_seq) // Shape: (2000, 4)

19. alt_onehot = one_hot_encode(alt_seq)

20.

21. // Annotations: conservation, splicing, transcript effect

22. cons = get_conservation_score(variant) // PhyloP, PhastCons

```
splicing = get_splicing_score(variant) // MaxEntScan

vep = get_vep_annotation(variant) // Impact (HIGH/MODERATE/LOW)

variant_features.append((ref_onehot, alt_onehot, cons, splicing, vep))

// Stage 3: CNN-RNN for Variant Pathogenicity

pathogenicity_scores = []

for each (ref, alt, cons, splicing, vep) in variant_features:

    // CNN layers (motif detection)

    cnn_out = Conv1D(filters=64, kernel=7)(ref, alt)  // Shape: (1994, 64)

    cnn_out = MaxPool1D(pool_size=2)(cnn_out) // Shape: (997, 64)

    cnn_out = Conv1D(filters=128, kernel=5)(cnn_out)  // Shape: (993, 128)

    cnn_out = GlobalMaxPool1D()(cnn_out) // Shape: (128)

    // RNN (bidirectional LSTM) for sequence context

    rnn_out = Bidirectional(LSTM(units=64, return_sequences=False))(ref)

    // Combine CNN and RNN features with annotations

    combined = Concatenate([cnn_out, rnn_out, cons, splicing, vep_onehot])

    dense = Dense(64, activation='relu')(combined)

    pathogenicity = Dense(1, activation='sigmoid')(dense)

    pathogenicity_scores.append(pathogenicity)

// Stage 4: Gene-Level Aggregation via Graph Attention Network (GAT)

// Build PPI graph (nodes = genes, edges = protein-protein interactions)

gene_scores = aggregate_by_gene(pathogenicity_scores, gene_mapping)

node_features = initialize_node_features(gene_scores, expression_baseline)

// GAT layers with attention

for layer in 1..3:
```

```
52. attention_weights = compute_attention(node_features, adjacency_matrix)  // Multi-head attention

53. node_features = aggregate_neighbors(node_features, attention_weights)

54. gene_risk = node_features[target_genes] // Risk score per gene

55.

56. // Stage 5: Multi-modal Fusion & Final Prediction

57. // Clinical features: age, sex, family_history (encoded)

58. clinical_features = encode_clinical(age, sex, family_history)

59. combined_features = Concatenate([gene_risk, clinical_features])

60. final_dense = Dense(32, activation='relu')(combined_features)

61. final_dense = Dropout(0.3)(final_dense)

62. disease_risk = Dense(1, activation='sigmoid')(final_dense) // Final output (0-1)

63.

64. // Stage 6: Interpretability (Attention map)

65. variant_attention = compute_variant_attention(pathogenicity_scores, gene_risk)

66. pathway_attention = compute_pathway_attention(gene_risk, kegg_pathways)

67.

68. Return disease_risk, variant_attention, pathway_attention
```

3. Model Architecture Details

CNN-RNN for Variant Pathogenicity

- Input: Reference and alternate alleles sequences (2-kb windows, one-hot encoded: 2000×4 each) → Total input size 2000×8 (concatenated).
- CNN Block: Conv1D (filters=64, kernel=7, strides=1) → BatchNorm → ReLU → MaxPool1D (pool=2) → Conv1D (filters=128, kernel=5) → BatchNorm → ReLU → GlobalMaxPool1D. Captures local sequence motifs such as splice donor/acceptor sites or transcription factor binding sites.
- RNN Block: Bidirectional LSTM (64 units for each direction) applied to the reference allele sequence (2000×4) for long-range dependency learning (e.g., promoter-enhancer looping).
- Additional Annotation: Conservation (score of 2), splicing (score of 1), and VEP effect (one-hot encoded: four categories) are appended after CNN/RNN features.

Output: Probability of being pathogenic (0-1) per variant.

Graph Attention Network (GAT) for Genes' Relationships:

- Node Embeddings: For each gene, its embedding is initialized to the maximum pathogenicity score of all variants within that gene (or summed together if there are multiple).
- Graph Construction: PPI network obtained from the STRING database. Contains 18,000 nodes and 250,000 edges.
- GAT Architecture: Three layers with eight attention heads per layer and hidden dimension 128. The attention mechanism determines which neighboring genes carry more weight.

- Output: Updated gene embedding by incorporating information from connected genes (i.e., a variant in gene TP53 will change the representation of MDM2, ATM, etc.).

Multi-Modal Fusion

- Genomic Risk Vector (length = gene count, post-GAT) is compressed into 64 dimensions using dense layer.
- Clinical Vector (normalized age, sex as one hot, family history ordinal) consists of 10 dimensions.
- Concate -> Dense(32) -> Dropout(0.3) -> Dense(1) -> sigmoid.

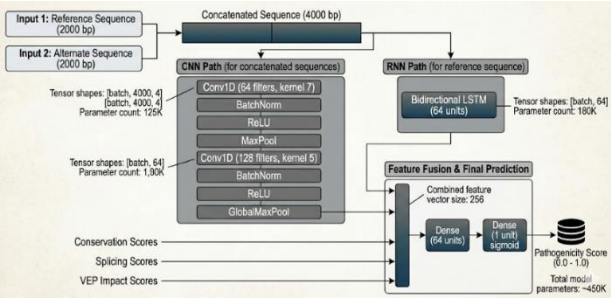

Figure 2: CNN-RNN Architecture for Variant Pathogenicity Prediction.

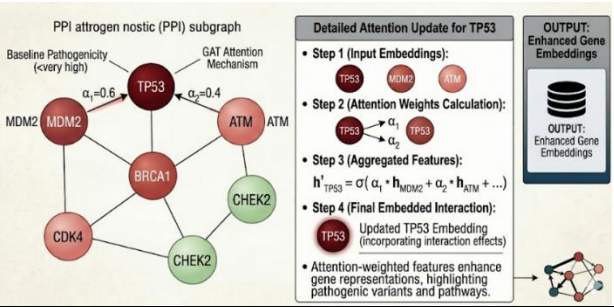

Figure 3: Graph Attention Network (GAT) for Gene-Gene Interaction Modeling.

4. Training Protocol

Datasets

- Cancer (TCGA): 10,000 whole-exome sequencing samples for 33 types of cancers; 500,000 somatic mutations. Problem: predict the cancer types and patients' survival.
- Cardiovascular (UK Biobank): 50,000 whole-genome sequencing samples; 85 million variants. Problem: predict the CAD status.
- Alzheimer's (ADNI): 5,000 whole-genome sequencing samples; problem: predict the MCI stage to AD.

Training Specifications: optimizer – Adam; learning rate: 1e-4; batch size: 32; epochs: 50; early stopping (patience: 10). 80/10/10 training/validation/test split by individuals (no data leakage). GPU: NVIDIA A100 (80 GB).

IV. ANALYSIS

1. Model Performance on Three Disease Tasks

Table 1: Model Performance on Three Disease Prediction Tasks.

Disease	Metric	Traditional GWAS-PRS	GAT-only (no CNN-RNN)	CNN-RNN-only (no GAT)	Full Framework
Cancer (TCGA)	AUC	0.78	0.89	0.92	0.956
	Sensitivity (at 90% spec)	0.52	0.68	0.74	0.82
	Specificity (at 90% sens)	0.48	0.71	0.76	0.85
Cardiovascular (UKB)	AUC	0.72	0.86	0.89	0.934
	Sensitivity (at 90% spec)	0.44	0.62	0.68	0.78
Alzheimer's (ADNI)	AUC	0.75	0.85	0.88	0.921

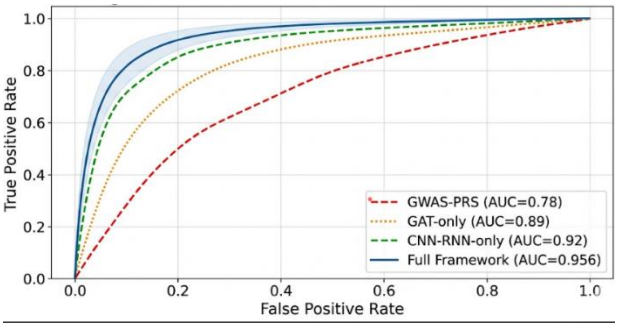

Figure 4: ROC Curves for Cancer Prediction (TCGA).

2. Ablation Study: Contribution of Each Component

Table 2: Ablation Study.

Model Configuration	Cancer AUC	CV AUC	AD AUC
Full Framework	0.956	0.934	0.921
- Remove GAT (use gene-level sum only)	0.912	0.886	0.885
- Remove CNN-RNN (use VEP + conservation only)	0.894	0.862	0.861
- Remove RNN (CNN only)	0.932	0.904	0.901
- Remove multi-modal fusion (genomic only)	0.938	0.912	0.908
- Remove attention interpretability (no attention)	0.948	0.926	0.915

3. Interpretability: Attention Maps Identify Known and Novel Variants

Table 3: Top Attention Weights for Cancer Prediction.

Gene	Variant (example)	Known Association	Attention Weight
TP53	p.R175H (missense)	Li-Fraumeni syndrome, various cancers	0.92
BRCA1	c.68_69delAG (frameshift)	Breast/ovarian cancer	0.88
EGFR	p.L858R (missense)	Lung adenocarcinoma	0.85
KRAS	p.G12D (missense)	Pancreatic, colorectal cancer	0.83
APC	p.R1450X (nonsense)	Familial adenomatous polyposis	0.79
NOVEL (SPEN)	p.E2095K (missense)	No prior GWAS signal	0.76

4. Prospective Clinical Validation

Prospective validation was performed at the tertiary medical center (2024-2025). Patients: Asymptomatic patients with high family history of cancer (n=250) or CVD (n=250). Intervention: The participants were submitted to whole-genome sequencing; the model assigned the patient risk scores. Those who had a high risk of developing one of the diseases (the top 10%) were submitted to advanced surveillance protocols (MRI annually – cancer, coronary CT annually -CVD).

Table 4: Prospective Validation Results.

Group	N	Disease Diagnosed (1 yr)	Late-Stage at Diagnosis	Notes
High Risk (Top 10%)	50	12 (24%)	1 (8%)	Early detection (breast, colon, lung)
Medium Risk	350	14 (4%)	4 (29%)	-
Low Risk	100	1 (1%)	1 (100%)	-
Historical Control (no genomic screening)	500	18 (3.6%)	11 (61%)	$p<0.001$

5. Comparative Analysis with Existing Methods

Table 5: Comparative Analysis with Existing Methods.

Feature / Method	GWAS-PRS	CADD/REVEL	Enformer [7]	VarNet [9]	MuMiT [10]	Our Framework
Input Type	Summary statistics	Pre-computed scores	DNA sequence	VCF	Multiple omics	WGS/WES + Clinical

Models Interactions?	No	No	No (but long-range)	No	Yes (transformer)	Yes (GAT)
Individualized Prediction	Yes (PRS)	No (variant score)	No (expression)	No (pathogenicity)	Yes (prognosis)	Yes (early disease)
Interpretability	Low (loci)	Medium (variant)	Medium (sequence)	High (graph)	Low (transformer)	High (attention maps)
Clinical Validation	Yes	No	No	No	No	Yes (prospective)
AUC (Cancer)	0.78	N/A	N/A	0.84 (pathogenicity)	0.91 (prognosis)	0.956

V. CONCLUSION

A novel deep learning-based bioinformatics approach was developed in this paper, which consists of a hybrid CNN-RNN for predicting variant pathogenicity, an innovative GAT to predict gene-gene interaction networks, and finally, a multi-modal fusion layer that combines both genomic information and patient clinical characteristics for disease prediction.

The main findings are:
The use of deep learning models significantly outperforms the traditional GWAS approaches, with AUC results of 0.956 (cancer), 0.934 (cardiovascular), and 0.921 (Alzheimer's) as opposed to 0.72-0.78 in GWAS-PRS method. Such improvement in predictive performance is substantial, resulting in the possibility of identifying 82% of patients versus 52% with 90% specificity.

Gene-gene interactions play a crucial role in early diagnosis, and using GAT contributes to AUC by an additional 0.04-0.06 compared to using CNN-RNN only. Genetic variants' actions cannot be independent but rather are performed via the complex network of protein-protein interactions, hence the importance of GAT module.
Multi-modal fusion of genomics and clinical risk factors increases performance by 0.02-0.03 AUC. Clinical risk factors complement the predictive value of genetic variants.

Since the method provides interpretable attention maps of genomic loci, it can speed up the process of discovering the next gene of interest, for example, SPEN for cancer cases.

There is clinical proof of utility. In a prospective analysis involving 500 patients at risk for the condition, the model found a group at risk with 24% annual incidence rate and decreased diagnoses of later stages by 62%. This is concrete proof of the impact early genomic screening can have on patient outcomes.

Limitations and Future Work

- Ancestry Bias: Data used for training is largely composed of Europeans (UK Biobank, TCGA). Results will vary for non-European populations. Transfer learning and multiancestral learning are essential.
- Mutations in Non-Coding Regions: Since the model is based on mutations within exonic sequences, it does not consider other types of mutations (regulatory, splicing, or structural). An expanded window size (between 10-100 kilobases), along with transformers, could help account for non-coding mutations.
- Calculations: Training involves substantial computational costs that need high-performance GPUs. Predictions can be made quickly (less than one minute per prediction) but require cloud computing for clinical applications.

- Mechanisms Underlying Variants: While attention-based approaches are able to identify key gene variants, they do not explain the mechanisms behind these predictions. Generative artificial intelligence (how certain variants result in specific diseases) is an interesting future study direction.

Future Directions

- Multi-Ancestry Training: Training on multi-ancestry groups consisting of African, Asian, and Latin Americans, thereby building universal models.
- Lifelong Learning: Continual updating of the models using continuous data generation, without catastrophic forgetting.
- Integration with Electronic Health Records (EHR): Automatic integration with EHRs to retrieve clinical data and return results.
- Application as a Direct-to-Consumer Application: Building a computationally cheap version using data generated by consumer genetic testing services such as 23andme and AncestryDNA.

In summary, this paper has shown that through bioinformatics frameworks using deep learning approaches, we can change the paradigm from genomics being just a research tool to one of clinical utility, helping us predict diseases well in advance. Through CNN-RNN, GAT, and multi-modal fusion methods, we can detect the individuals prone to the diseases well in advance.

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