Unlocking the Dark Genome: Multimodal Transformers for Predicting Non-Coding Variant Functionality in Precision Medicine

Abstract. Since most disease- and trait-associated genetic variants lie within non-coding regions, functional interpretation of these variants remains one of the central challenges in precision medicine. Recent deep learning models have begun to address this gap, though most existing models use only sequence information as input or are limited in the regulatory context they consider. We propose a multimodal transformer framework that takes as input nucleotide sequence, chromatin accessibility (ATAC-seq), histone modification profiles (H3K27ac, H3K4me3) and transcription factor binding signals to predict the regulatory effects of non-coding variants. Building on recent advances in DNA language modeling and locus-level regulatory predictions (e.g. the *Nucleotide Transformer* and other transformer-based genomic models), our model is specifically designed to capture long-range enhancer–promoter interactions, and context-specific regulatory signatures. We present the model architecture, genome-wide tokenization of k-mers, and multimodal fusion strategy to prioritize variants that alter regulatory function, thereby helping to unlock the "dark genome." This framework has direct relevance for neurodevelopmental and other complex disorders where the impact of non-coding mutation burden remains largely unexplored. We hope to provide a framework for the development of scalable and context-aware variant annotation tools capable of translating non-coding risk signals to mechanistic molecular insight.

1 Introduction

Coding sequence variation has been well studied. However, regulatory variation accounts for over 90% of disease-associated SNVs and far more difficult to interpret. Regulatory elements (promoters, enhancers, silencers and insulators) influence the information encoded in the genome by multilayered regulation of transcription factor (TF) binding, chromatin state and three-dimensional genome organization, leading to gene expression. Nonetheless, functional annotation of non-coding variants is largely restricted to sequence context and/or aggregated epigenomic signals, without taking into account long-range regulatory coupling or tissue-specific regulatory dynamics.

Conversely, transformer-based deep learning architectures, initially developed for natural language processing, have demonstrated strong performance in various genomics applications. By treating DNA as a "text", models such as the Nucleotide Transformer show that unsupervised pre-training on large genomic corpora leads to context-aware representations, which can be further fine-tuned for downstream tasks such as variant prediction even with limited labeled data. The long-range and multi-scale dependencies captured by transformers closely mirror the biological reality of distal regulatory interactions and enhancer–promoter communication.

Despite these developments, very few models leverage sequence and rich regulatory context in a single architecture (and even fewer in a systematic way to predict variant effects within noncoding regions). Here we present a conceptually informed multimodal transformer model that combines nucleotide token embeddings with chromatin accessibility, histone modification, and transcription factor (TF) occupancy maps to enable context-aware interpretation of noncoding variation. We hypothesize that this framework can order variants by their predicted effect on regulatory function, offering a new step toward decoding the "dark genome".

2 Related work

Early research demonstrated that gene function and the influence of genetic variation could, to some extent, be inferred directly from DNA sequence. Using a type of system called convolutional architecture, like DeepSEA [1] and Basset [2], they demonstrated that computers could learn to anticipate where proteins bind, which areas are open to access, alongside various markers, just from the sequence. Consequently, these systems assess how changes in single letters of the code might affect gene regulation. Early studies showed we could decipher genetic control signals just by looking at DNA sequences, though their view was restricted, they couldn't see the big picture.

Later designs got sharper alongside better understanding; BPNet [3], for example, revealed how individual building blocks cooperate while reading DNA directly. Similarly, approaches like Sei [4] tackled multiple tasks simultaneously, connecting sequences to diverse cellular actions throughout numerous kinds of cells. Discovering patterns in DNA alongside what those patterns do saw substantial progress, though most approaches focus on nearby genetic code instead of direct tests of regulation.

A major leap occurred with architectures capable of modeling long-range genomic interactions, crucial for enhancer–promoter communication. Systems like Enformer [5] and Basenji2 [6] can consider huge stretches of DNA, up to megabases, which greatly improves predictions of gene activity by accounting for distant influences and where things are located. Researchers using Enformer showed how considering extensive genetic sequences boosts accuracy when predicting gene activity, a key issue previous computer systems struggled with. Yet, even these advanced systems don't naturally combine sequence data alongside crucial lab results like ATAC or ChIP information, limiting their grasp of what's happening inside cells.

Meanwhile, other projects such as DNABERT [7] and Nucleotide Transformer [8] revealed that training computers on huge amounts of genetic code first creates versatile tools capable of improving predictions when labeled data is scarce. Models excel at applying knowledge from one area to another, improvements in how they understand language and DNA building blocks help a lot. They offer a solid starting point when working with limited biological data. However, even these advanced models, built solely on genetic code, require additional lab results to accurately predict what happens inside cells.

Newer studies now integrate genetic information alongside epigenetic factors or other key indicators. Researchers are building systems, like EpiGePT [9], that blend

data on gene activity, how DNA folds, alongside epigenetic information within transformer models. The goal was to achieve better forecasts of cell-specific chromatin behavior and improved performance across different cell types. Integrating experimental details, ATAC-seq results, histone patterns, TF status, Hi-C maps, boosts predictions regarding regulatory effects while improving the interpretability of variant effects. Nevertheless, comprehensive models directly combining DNA sequences with detailed epigenomic data through a unified transformer remain relatively new.

Models that draw on evolutionary changes or other alternative strategies offer unique benefits. They pinpoint harmful mutations even without lab data, frequently boosting what standard prediction tools do when assessing health impacts from gene changes. However, these evolutionary clues miss crucial details: where in the body an effect happens, or how activity levels shift during development. This creates a knowledge gap.

Early neural networks showed potential, yet struggled with distant relationships within DNA. Later transformers excelled at spotting those connections, though they often ignored crucial epigenetic data. While large language models offer helpful patterns, they require combining different kinds of information to truly understand biology. Recent multimodal transformers are encouraging; however, a comprehensive system, one that smartly handles genomic code, integrates datasets like ATAC/histone/TF signals, then predicts how genetic changes impact cells across various tissues, remains undeveloped.

This motivates our approach, which aims to tackle this challenge by merging strong sequence analysis, reusable learning, and detailed epigenetic insights, ultimately helping pinpoint impactful variations in non-coding regions.

Table 1. Representative Deep Learning Models for Regulatory Function Prediction and Variant Interpretation

Model	Year	Input Modalities	Architecture	Capture LongRange Dependencies	Variant Scoring	Key Limitation
DeepSEA (Zhou & Troyanskaya)	2015	DNA sequence (1kb)	CNN	No	Yes	Limited to local sequence context; lacks 3D interactions
Basset (Kelley et al.)	2016	DNA sequence (600 bp)	CNN	No	Yes	Cell-type-specific predictions limited; no chromatin data
BPNet (Avsec et al.)	2019	DNA sequence + TF ChIP-seq	CNN-based with dilated conv	No	Yes	Accurate at motif level but lacks long-range modeling
Enformer (Avsec et al.)	2021	DNA sequence (200 kb)	Transformer + CNN hybrid	Yes	Yes	Sequence-only; does not integrate epigenomic modalities
DNABERT (Ji et al.)	2021	DNA k-mers (3-6 mers)	BERT Transformer	No	Yes	Focused on sequence text modeling; no multimodal context

Nucleotide Transformer (Dalla-Torre et al.)	2023	Genomic sequence (1 bp tokens)	Large Transformer (2.5 B params)	Yes	Yes	Sequence-only pretraining; lacks regulatory data integration
EpiGePT (Zhou et al.)	2023	Sequence + Epigenomic tracks (ATAC, H3K27ac, TFBS)	Multimodal Transformer	Yes	Yes	Context-limited; trained on small cell-type subset
Basenji2 (Kelley)	2024	DNA sequence (1 Mb)	CNN-Transformer hybrid	Yes	Yes	No explicit variant prioritization module
Our Proposed Model	2025	Sequence + ATAC-seq + Histone marks + TF binding	Multimodal Transformer	Yes	Yes	Designed to unify regulatory context for variant interpretation

3 Proposed Model Architecture and Methodology

3.1 Overview

We propose the Genome-Scale Multimodal Transformer GMT: A Conceptual Framework—a framework designed to integrate nucleotide sequence information with four other complementary genomic modalities, chromatin accessibility assessed by ATAC-seq, histone modification profiles H3K27ac and H3K4me3, and transcription factor occupancy maps, for predicting the potential regulatory impact of non-coding variants.

Different from the traditional unimodal architectures, GMT is designed to fuse sequence-derived representations with aligned epigenomic channels in a single transformer backbone. Moreover, this can really help the model capture higher-order dependencies between sequence motifs and chromatin state for more context-aware interpretation of non-coding variation [11]. Complemented by unified attention mechanisms, GMT establishes a connection between nucleotide-level information and tissue-specific regulatory architecture.

3.2 Input Representation and Tokenization

Sequence Encoder. Each genomic window (±50 kb around a variant) is conceptually tokenized into overlapping k-mers (k = 6–8) with a stride of one base. Each token would correspond to a learned embedding vector initialized via standard schemes such as Xavier uniform initialization [19]. To preserve the linear genomic order, sinusoidal positional encodings [11] would be incorporated, yielding a sequence tensor $S \in \mathbb{R}^{N \times d_{\text{model}}}$.

Epigenomic Encoder. Epigenomic inputs, including ATAC-seq accessibility, histone marks (H3K27ac, H3K4me3), and TF-ChIP–seq tracks, would be aligned to fixed genomic bins (e.g., 50 bp), quantile-normalized, and Z-score–scaled [20]. Each signal channel could then be projected into the same latent dimensionality as the sequence embeddings through modality-specific linear projections, resulting in modality embeddings $E_i \in \mathbb{R}^{N \times d_{model}}$.

These embeddings would be concatenated across a new modality axis to form a unified multimodal input tensor.

3.3 Multimodal Transformer Encoder

The newly proposed architecture consists of multi-layered transformers that might be composed of, for instance, L = 24 layers, each consisting of multi-head attention H=16, feed-forward sub-layers, and residual normalization.

Contrary to the unimodal genomic transformers, GMT would use cross-modal self-attention, permitting direct interactions between nucleotide motifs and their interacting chromatin features.

Such a Hi-C–guided attention prior could introduce additional biological realism by penalizing attention beyond empirically supported genomic contact distances, for example, ≤200 kb [21].

It balances biological interpretability with the expressive capacity needed for regulatory inference.

3.4 Variant Scoring and Prediction Head

In the proposed framework, a designated [CLS] token embedding from the final transformer layer would serve as a global representation of the genomic window.

This vector could be passed through a two-layer feed-forward network ($d_{model} \rightarrow d_{model}/2 \rightarrow 1$).

with GELU activation and sigmoid output, yielding a probabilistic estimate $p(v) \in [0,1]$ for variant disruption.

A conceptual loss formulation integrating classification, ranking, and regularization objectives can be expressed as:

$$L = \lambda_1 BCE(p, \hat{y}) + \lambda_2 RankLoss(p_i, p_j) + \lambda_3 ||\theta||_2^2$$

where $\hat{y}$ represents binary variant labels and the ranking term ensures correct prioritization when only relative functional labels are available [13].

3.5 Training Strategy

Pre-training (Unsupervised). Using a fully implemented environment, GMT could be pre-trained using a masked-token reconstruction objective similar to that used by BERT [22], masking roughly 15% of k-mer tokens and predicting them from context. The pre-

training corpus would ideally span both the GRCh38 reference genome and an extensive set of non-coding loci so as to engender generalizable representations of regulatory syntax.

Fine-Tuning (Supervised). Supervised fine-tuning would utilize curated variant-function datasets such as MPRA, eQTL, and saturation-mutagenesis assays [15], stratified by tissue type to preserve biological specificity. Early stopping can be guided by validation AUROC and PR-AUC metrics. For large-scale training, one can make full use of various computational efficiency optimization strategies such as mixed precision and gradient checkpointing.

3.6 Interpretability and Attribution

To enable mechanistic interpretation, post hoc techniques such as attention attribution and Integrated Gradients [16] can be applied to highlight which sequence motifs or epigenomic bins most strongly influence model predictions.

For example, strong attribution to a disrupted TATA-box motif within an active enhancer could imply altered promoter looping or transcription initiation [17].

3.7 Implementation and Scalability

While conceptual, GMT is designed to be computationally tractable for genome-scale inference.

A reference implementation could employ PyTorch with distributed data parallelism and mixed-precision training to accommodate long genomic windows (up to 100 kb, ≈20k tokens).

A model of this size (~400M parameters) would be suitable for large-scale variant prioritization across tissues, potentially supporting inference times on the order of milliseconds per variant when optimized on modern GPUs.

Such scalability positions GMT as a practical framework for the next generation of multimodal precision genomics models [17].

4 Experimental Setup

4.1 Benchmark Datasets

To evaluate the proposed Genome-Scale Multimodal Transformer (GMT), we outline a set of benchmark datasets widely used in regulatory genomics:

- **ENCODE Project** [18]; provides ATAC-seq and histone modification (H3K27ac, H3K4me3) profiles across multiple tissues.
- **Roadmap Epigenomics** [19]; defines enhancer–promoter landscapes and tissue-specific chromatin states.
- **gnomAD and ClinVar** [20]; catalog non-coding variants annotated by disease association and allele frequency.

Together, these resources represent complementary biological dimensions: regulatory activity (ENCODE), chromatin architecture (Roadmap), and variant-level phenotypic associations (ClinVar, gnomAD).

4.2 Data Preprocessing

Each candidate variant is represented as a ±50 kb genomic window, tokenized into overlapping 6-mers. Epigenomic signals from ATAC-seq and histone marks are quantile-normalized and aligned to 50 bp bins to ensure consistent spatial resolution. Missing regions are linearly interpolated across flanking bins, and all tracks are harmonized to the hg38 genome assembly.

To mitigate tissue imbalance, random subsampling is performed to maintain equal representation across cell types. The final dataset comprises roughly 8 million variant-centered windows for training and 1 million for validation and testing.

4.3 Training Configuration

The model follows a two-stage optimization strategy:

- **Unsupervised pre-training.** Masked k-mer reconstruction over the GRCh38 genome (analogous to BERT [22]) using AdamW with a learning rate of 1e−4, batch size 4, and dropout 0.1.
- **Supervised fine-tuning.** Predicting variant functionality using curated datasets such as MPRA and eQTL benchmarks [15].

All runs employ mixed-precision training and distributed data parallelism. Early stopping is based on validation AUROC, with model checkpoints saved every 5 epochs.

4.4 Baselines for Comparison

To contextualize GMT's design, we reference three widely recognized architectures:

- **DeepSEA** [11] and **Basset** [12]: early CNN models that learn motif-level regulatory codes.
- **Enformer** [5]: long-range transformer capturing distal enhancer–promoter interactions.
- **EpiGePT** [19]: multimodal transformer leveraging chromatin context.

GMT unifies these directions by modeling both nucleotide-level features and epigenomic signals within a shared attention space.

4.5 Evaluation Metrics

To ensure robust and interpretable evaluation, the following metrics are employed:

- AUROC (Area Under Receiver Operating Characteristic Curve); measures global classification performance.
- AUPRC (Area Under Precision–Recall Curve); evaluates performance on imbalanced datasets.
- Pearson correlation; quantifies correspondence between predicted and observed chromatin signal intensities.
- Variant ranking accuracy; measures the correct prioritization of pathogenic vs. benign variants.

Metrics are reported as mean ± standard deviation across 5-fold cross-validation. Although full-scale experiments are deferred, this configuration ensures comparability with prior genomic transformer baselines [5, 14].

Note: The experimental setup described here is conceptual, outlining the intended evaluation framework for future implementation. No empirical training or benchmarking has been performed within the current scope of this work.

5 Anticipated Results and Discussion

5.1 Expected Performance

The Genome-Scale Multimodal Transformer (GMT) is anticipated to perform better than previous sequence-only and epigenome-only models in predicting the effects of non-coding variants due to its architecture.

GMT is expected to improve the AUROC scores for Enformer [5] (≈0.89) and EpiGePT [9] (≈0.90) by combining nucleotide-level context with chromatin state information, thereby increasing its discriminatory power on regulatory variant classification tasks.

It is anticipated that the combination of multimodal attention and Hi-C-guided regularization will improve interpretability and cross-tissue generalization.

5.2 Tissue-Specific Generalization

Tissue-specific regulatory dependencies, such as the enrichment of HNF4A and CEBPA motifs in hepatic tissues or REST and SOX2 in neural contexts, are expected to be captured by GMT's multimodal attention mechanisms.

When compared to unimodal architectures, this capability should produce better correlation between predicted and observed chromatin accessibility patterns, which is consistent with improvements noted by earlier multimodal frameworks [9].

5.3 Interpretability and Mechanistic Insights

It is anticipated that attention attribution and integrated gradients [16] will produce maps that are biologically interpretable and localize the significance of variants to known enhancer or motif regions. GMT may offer mechanistic explanations for how

particular non-coding variants affect cis-regulatory grammar by matching high-attribution sites with verified enhancers (like VISTA) and CTCF binding sites.

The model should also implicitly recover chromatin loop interactions that are consistent with empirical contact maps, as Hi-C priors limit long-range attention [21].

5.4 Ablation Expectations

Ablation analyses are expected to confirm the necessity of both modalities.

Removing epigenomic channels would likely reduce variant classification performance, whereas removing sequence embeddings would impair fine-grained motif sensitivity.

Similarly, omitting Hi-C–based regularization might increase overfitting and reduce cross-tissue transferability.

5.5 Comparative Positioning

GMT is a synthesis of nucleotide-level representation learning and epigenomic modulation in a shared attention space, in contrast to Enformer [5] and EpiGePT [9].

Where Enformer emphasizes distal sequence dependencies and EpiGePT emphasizes epigenomic context, GMT unifies both to achieve a richer understanding of gene regulation.

This integration is expected to yield more biologically coherent predictions and interpretable variant prioritization.

5.6 Limitations and Future Work

Despite its conceptual promise, GMT's scale (≈400M parameters) imposes training challenges, and the reliance on high-quality multi-tissue data may limit coverage for rare cell types.

Future extensions could incorporate cross-species transfer learning [8, 14] and multi-omics fusion (e.g., methylation, proteomics) to broaden generalizability.

The ultimate goal of GMT is to provide a foundation architecture for the interpretation of zero-shot variants in tissues that have not yet been characterized.

6 Conclusion

The Genome-Scale Multimodal Transformer (GMT) represents a step toward a unified architecture for decoding the non-coding genome.

By jointly embedding nucleotide sequence, chromatin accessibility, and histone modification signals into a shared transformer attention space, GMT provides a biologically principled mechanism to model regulatory logic at base-pair resolution.

Unlike prior unimodal frameworks that focus either on DNA sequence [11] or isolated epigenomic modalities [18], GMT's multimodal fusion allows context-aware reasoning, capturing both motif-level and higher-order chromatin interactions within a single scalable model.

Even though extensive empirical validation is still a work in progress, GMT's design foresees a number of benefits:
(1) improved generalization across tissues through cross-attention alignment of sequence and epigenomic channels;
(2) enhanced interpretability via attention-based attribution maps constrained by Hi-C priors [21]; and
(3) extensibility to additional data modalities such as methylation, RNA-seq, and proteomics, enabling richer functional annotation of the non-coding genome.

Frameworks such as GMT have the potential to accelerate variant-to-function mapping in the context of precision medicine, revolutionizing the interpretation of non-coding mutations in disease genomics.

This work lays the groundwork for future genomics foundation models that can integrate with large patient datasets, transfer across species, and perform zero-shot inference by combining transformer-based representation learning with biologically grounded inductive biases [8, 14].

Ultimately, GMT aspires not only to predict, but to explain, bridging the gap between sequence variation and regulatory consequence, and advancing the long-term vision of interpretable, genome-wide AI systems for human health.

7 References

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