Identifying the DNA binding specificity of chromatin complexes in leukaemia

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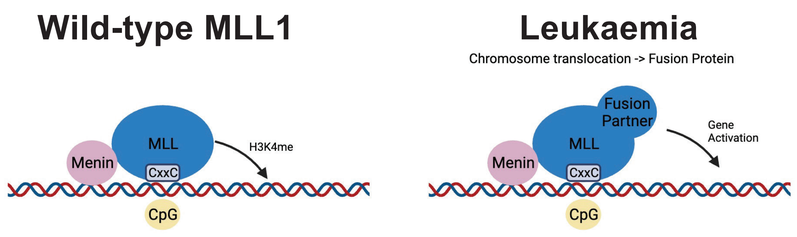
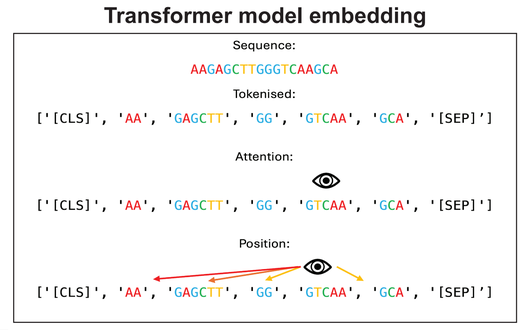
1. Introduction

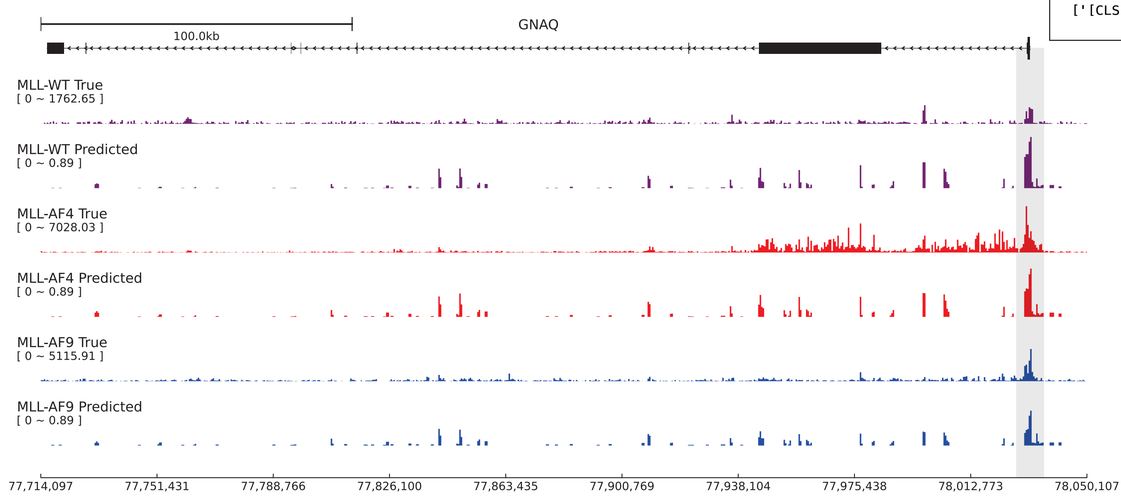


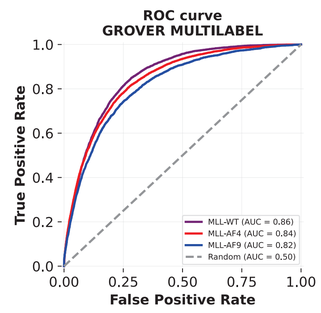
Wild-type MLL1 (KMT2A) and the oncofusion proteins MLL-AF4 and MLL-AF9 share an N-terminus that contains a CxxC domain for binding unmethylated CpG dinucleotides essential for the recruitment of MLL-WT and MLL-FPs to specific gene promoters, however, not every CpG island is bound by MLL-AF4. Moreover, MLL-AF4 also binds outside of uCpGs[1].

2. MLL Binding can be predicted from sequence

To establish if DNA sequence is important for MLL-WT or MLL-FP binding, a binary multi-label classification transformer model[2] was fine-tuned with MLL1 CUT&TAG peaks in MLL-WT (RCH-ACV), MLL-AF4 (SEM), or MLL-AF9 (THP-1) cells. MLL1 binding was predicted with high accuracy (ROC AUC > 0.82) by the model.

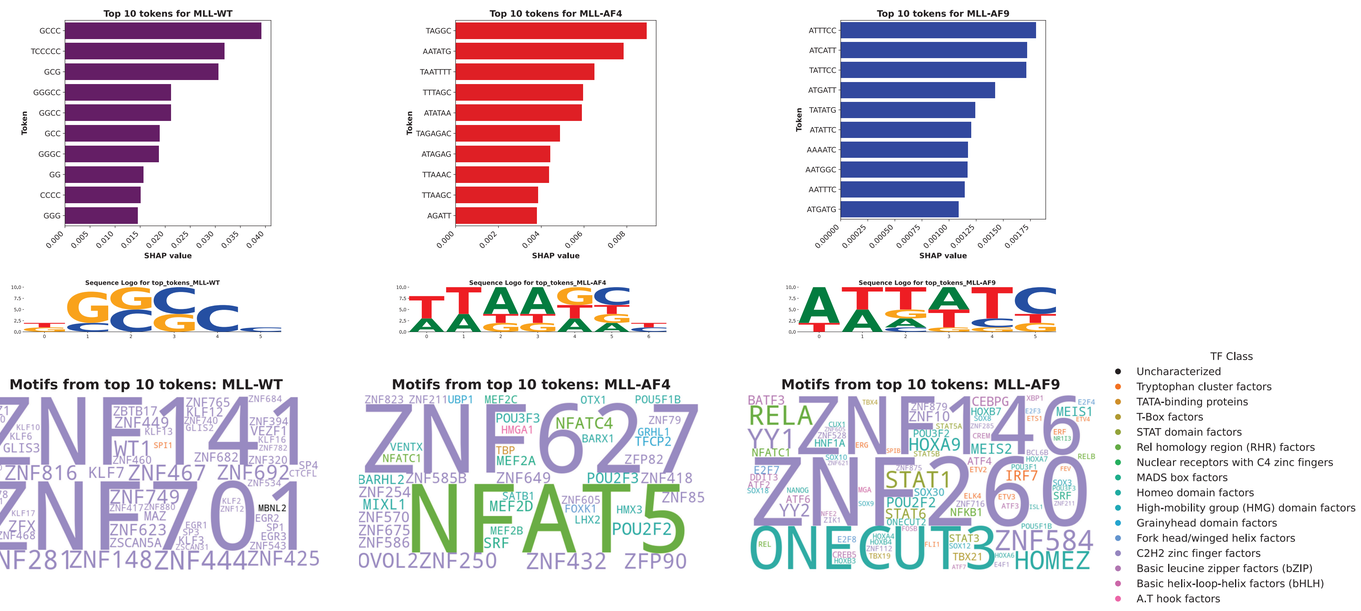






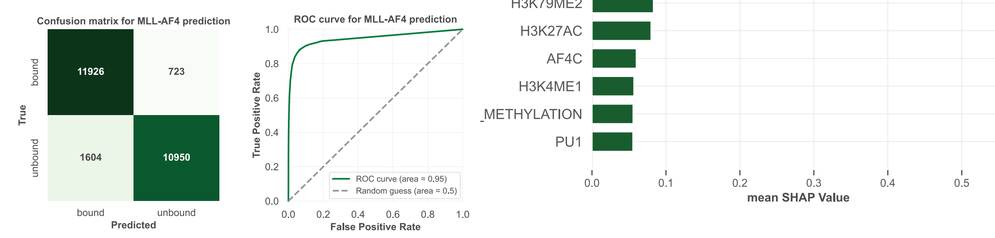
3.MLL-WT has a preference for CG rich sequences

The key tokens (K-mers) for predicting MLL-WT, MLL-AF4 or MLL-AF9 binding were extracted using SHAP[3] from the trained transformer model. Multiple sequence alignment indicated MLL-WT has a preference for CG rich sequences, whereas the most important sequence features for MLL-FPs were AT rich.

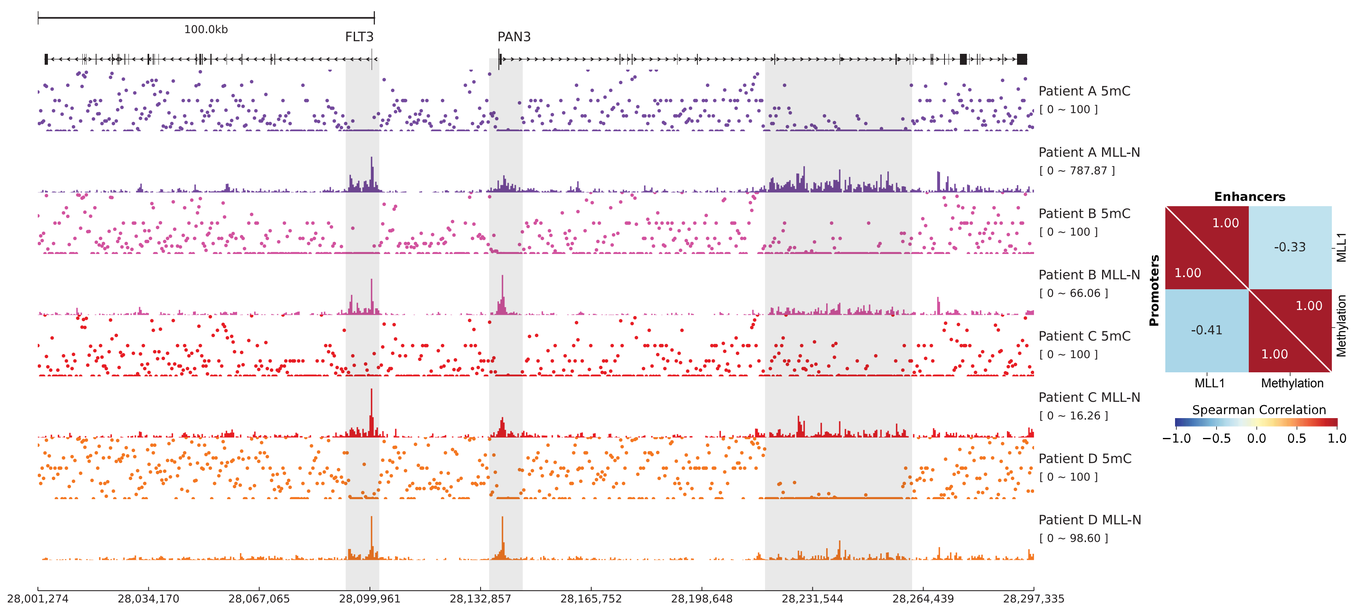


4. Epigenomic landscape influences MLL-AF4 binding

For determining which aspects of the epigenomic landscape are important for MLL-AF4 binding, a GBM classifier was trained to predict MLL-AF4 binding given a panel of 63 features. The model accurately (ROC AUC of 0.95) predicted MLL-AF4 and confirmed that uCpGs along with ERG and RUNX2 were highly important for determining MLL-AF4 binding.



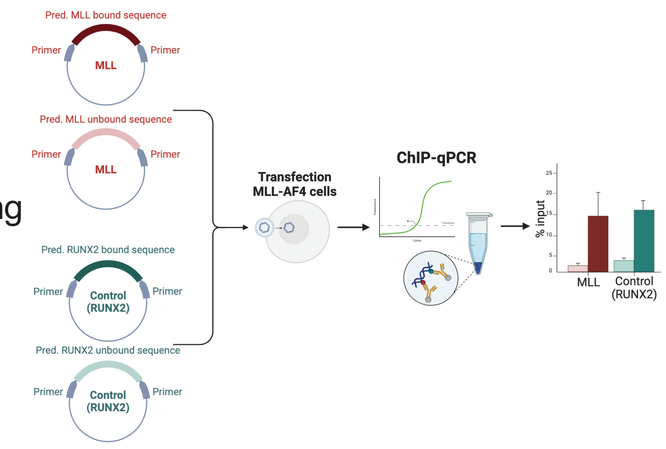
5. Methylation mirrors MLL-AF4 binding



Targeted simultaneous SNV and methylation status sequencing[4] in MLL-AF4 blast samples showed a striking inverse correlation with MLL-AF4 binding, which appears to be stronger at both promoters and enhancers compared to other inter- or intra-genic regions in MLL-AF4 cells.

6. Validation of predicted binding

Our findings enhance the understanding of how specific DNA sequences and the epigenomic landscape contribute to the unique binding patterns of MLL-AF4. Future work will combine these aspects into a unified model and validate the model predictions *in vivo*.



7. References

1. Kerry, J., et al. (2017) *Cell Reports*
2. Sanabria, M., et al. (2024) *Nature Machine Intelligence*
3. Lundberg, S and Lee, S. (2017) *NeurIPS Proc.*
4. Füllgrabe, J. (2023) *Nature Biotechnology*