

Integrative Analysis Reveals Histone Demethylase LSD1 Regulates RNA Polymerase II Pausing

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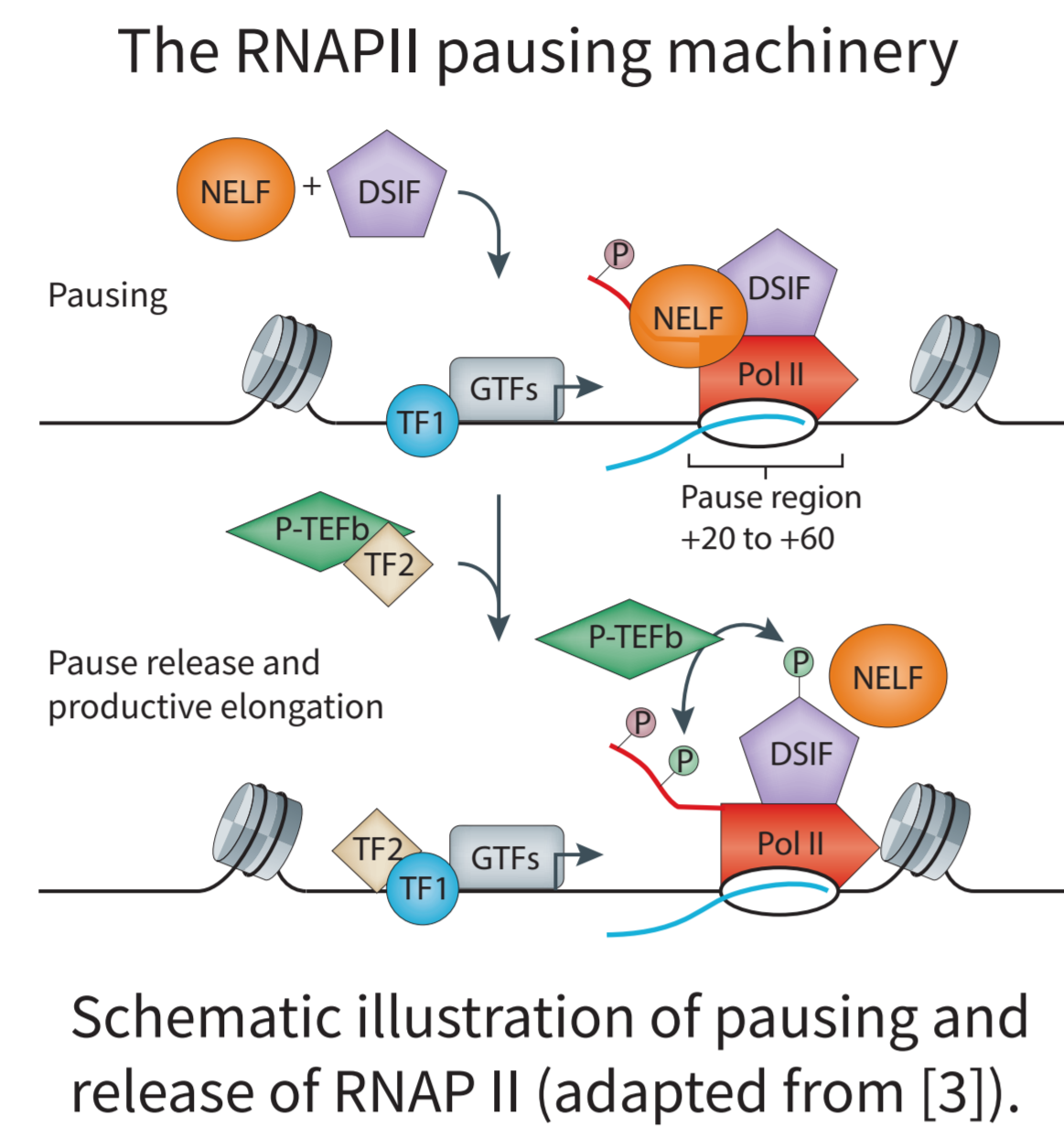
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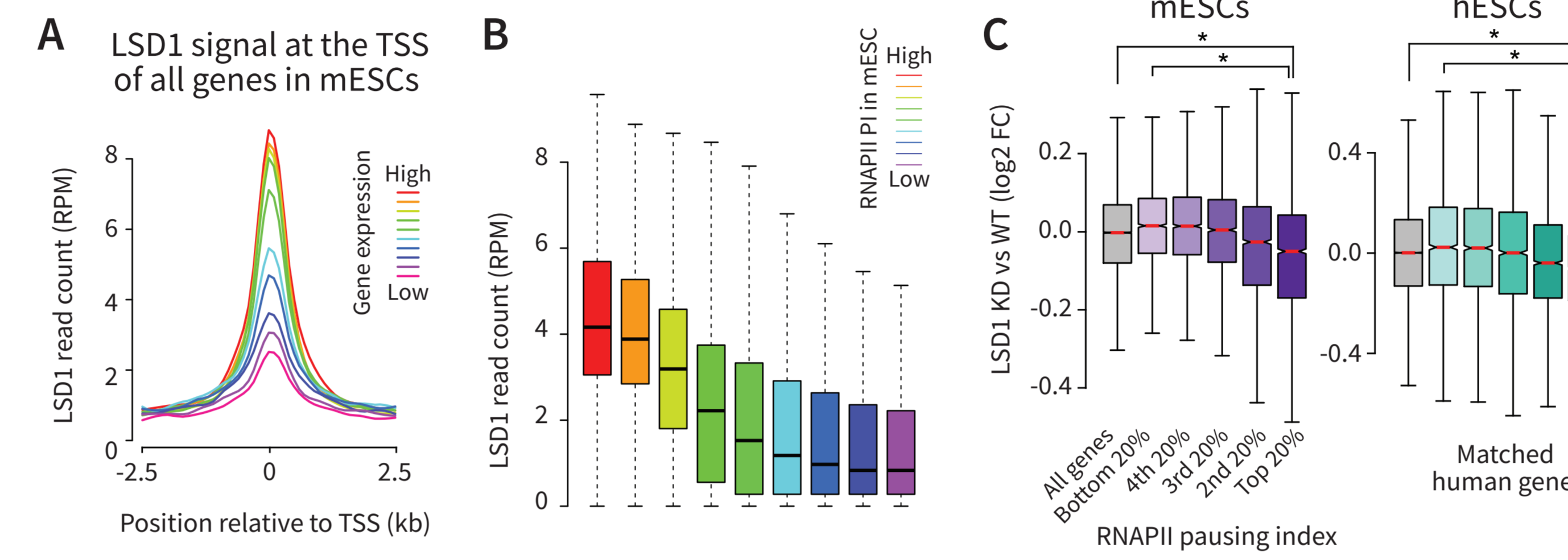
Background

RNA polymerase (RNAPII) pausing at the promoter of genes is a rate-limiting step in transcriptional regulation [1]. The coordinated actions of pausing and releasing factors collectively modulate RNAPII pausing. The involvement of chromatin remodellers such as the histone lysine-specific demethylase 1 (LSD1) in RNAPII pausing has not been well documented. Whilst LSD1 is well-known for its role in decommissioning enhancers during ESC differentiation in mouse (mESC) [2], its role at promoters of genes remains largely unknown.

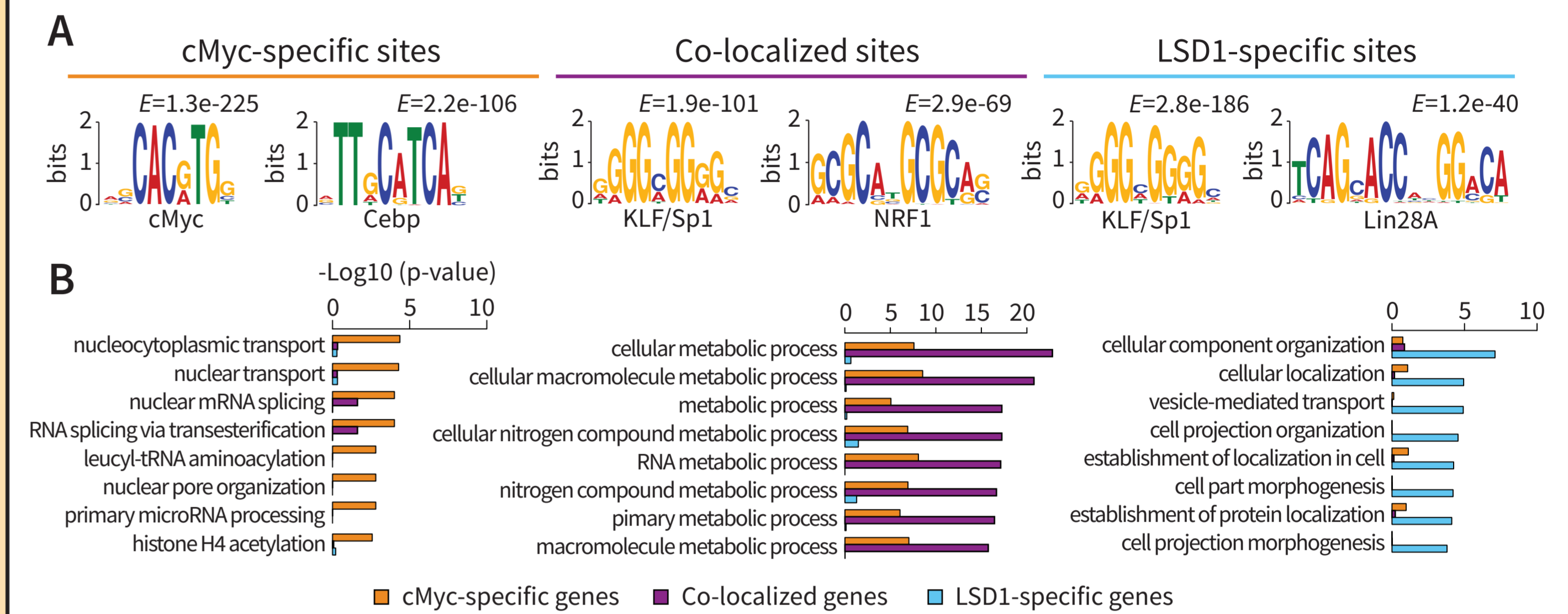
Here, we perform an integrative analysis to present evidence for a previously unanticipated role of LSD1 as a regulator of RNAPII pausing through.



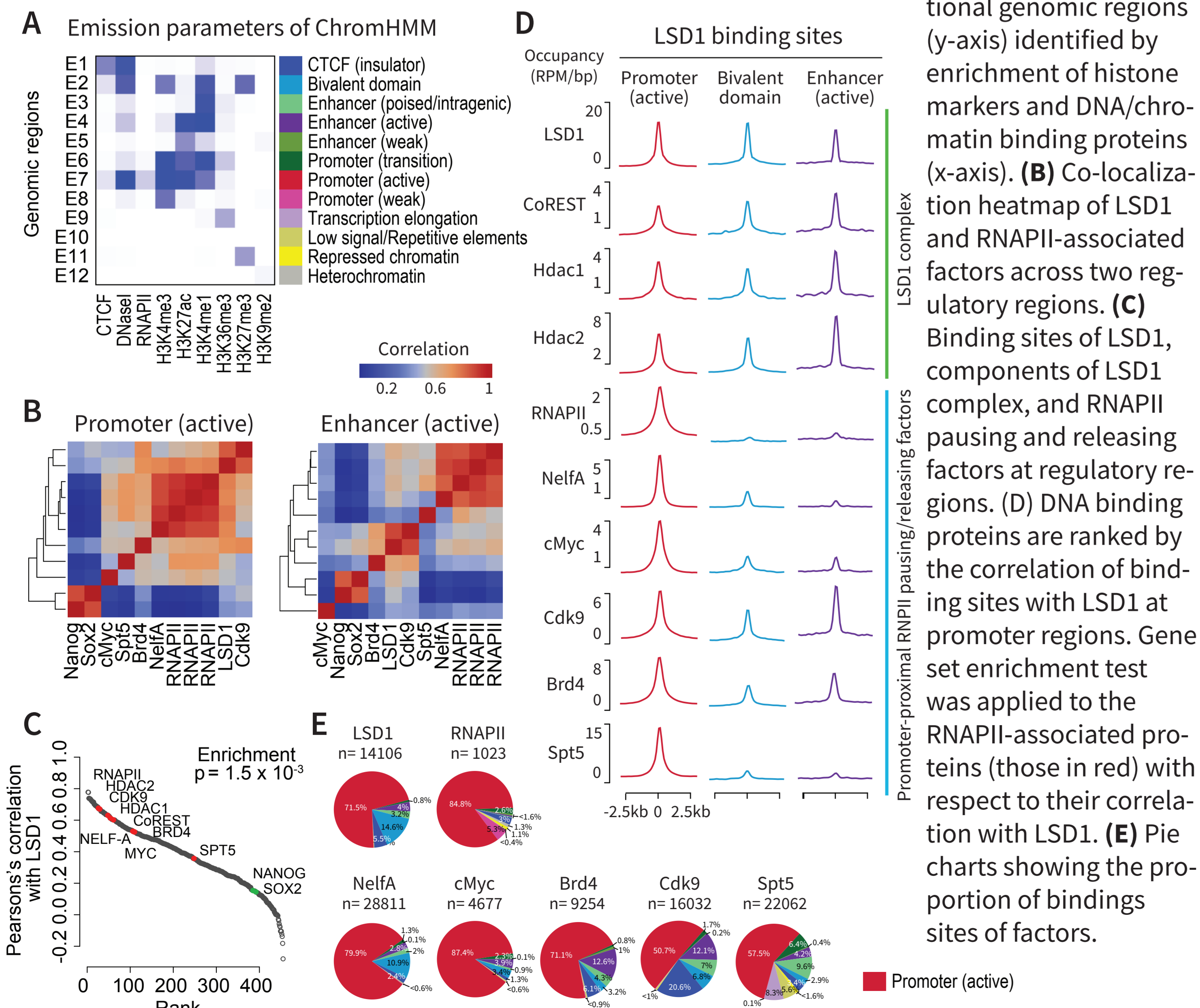
LSD1 knockdown affects genes with higher RNAPII pausing than those with lower pausing



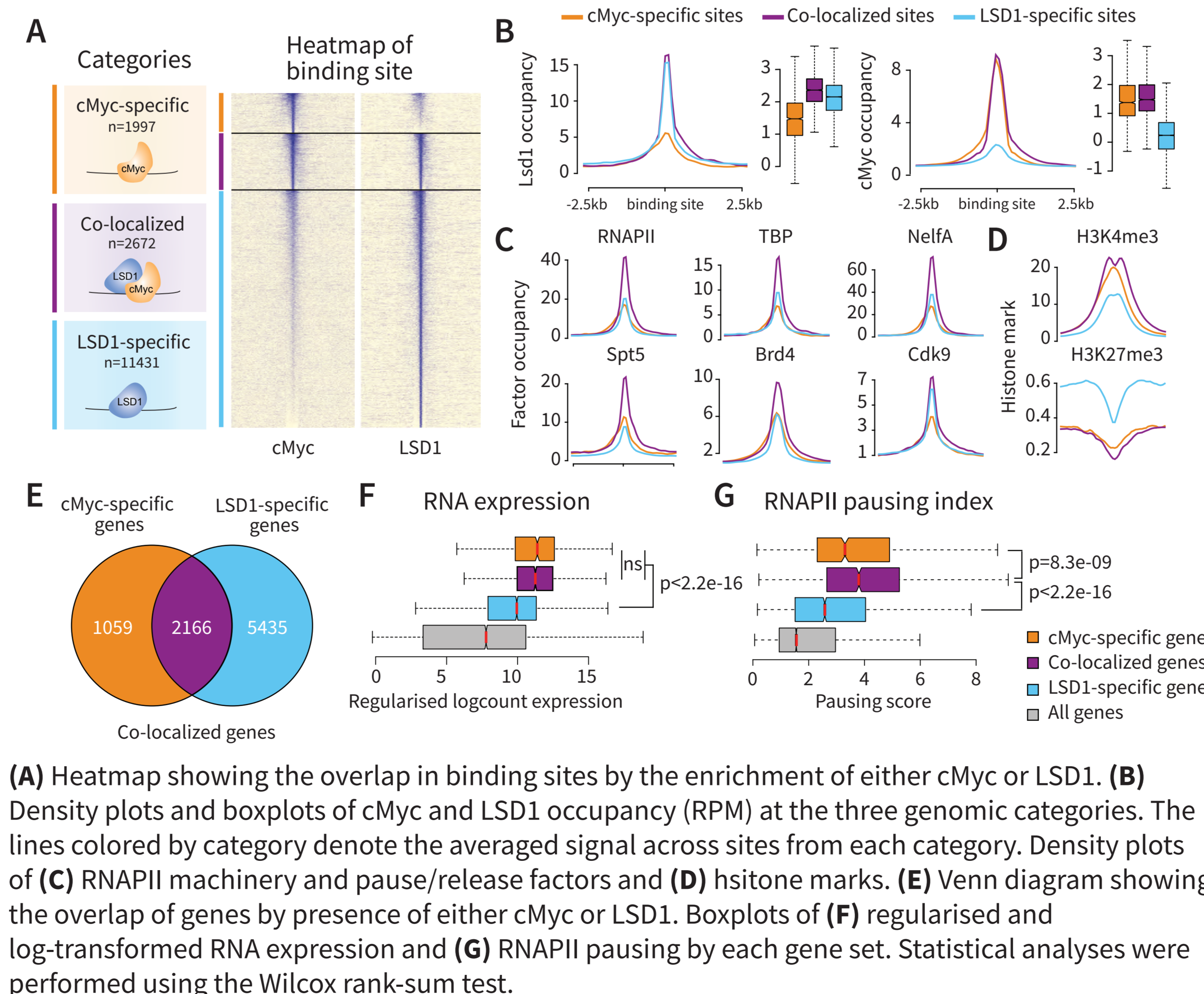
LSD1 sites are differentially enriched for cell-type specific and housekeeping genes



LSD1 co-localizes with RNAPII pausing machinery at active promoters



LSD1 and cMyc co-occupied sites are enriched for RNAPII pausing factors



Conclusions

Our integrative analysis implicates LSD1 as a regulator of RNAPII pausing at the promoter of genes in mESCs. We propose that LSD1 may modulate the release of paused RNAPII through its association with key pause release factors, Cdk9 and cMyc, and demonstrate the functional enrichment of transcription factors and housekeeping genes by LSD1 and cMyc occupancy.

Acknowledgements and References

[1] Core, L. & Adelman, K. Promoter-proximal pausing of RNA polymerase II: A nexus of gene regulation. *Genes and Development* (2019). [2] Whyte, W. A. et al. Enhancer decommissioning by LSD1 during embryonic stem cell differentiation. *Nature* (2012). [5] Adelman, K. & Lis, J. T. Promoter-proximal pausing of RNA polymerase II: emerging roles in metazoans. *Nat. Rev. Genet.* 13, 720–731 (2012). [6] Foster, C. T. et al. Lysine-Specific Demethylase 1 Regulates the Embryonic Transcriptome and CoREST Stability. *Mol. Cell. Biol.* (2010). [7] Adamo, A. et al. LSD1 regulates the balance between self-renewal and differentiation in human embryonic stem cells. *Nat. Cell Biol.* (2011).

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