Inserting L1 sequences on a transcript leads to decrease in RNA expression via inadequate transcript elongation,[25] and this effect has been attributed to the A/T enrichment of L1s. However, our results argue that transcriptional attenuation of host gene expression could be a consequence of epigenetic silencing by HUSH/MORC2 (Fig. 4b,c and Extended Data Fig. 9d-g, 10a), and this possibility is consistent with the described role of genic H3K9me3 in decreasing Pol II elongation rate, leading to its accumulation over the H3K9me3 region[26]. If such mechanism is at play, then HUSH KO should decrease accumulation of the elongating Pol II over L1 bodies, and this is indeed what we observe in Pol II ChIP-seq experiments (though interestingly, at 5' UTRs of L1s, Pol II levels are relatively elevated in the KOs) (Extended Data Fig. 10b).

Importantly, host gene regulation is directly dependent on the presence of the intronic L1, as deletion of select MORC2/HUSH-bound L1s from the intron led to the upregulation of host mRNA to a level commensurate with the magnitude of changes caused by HUSH/MORC2 KO (Fig. 4d,e and Extended Data Fig. 10c,d). Thus, dampening expression levels of an active gene can be a by-product of a retrotransposition event and associated HUSH/MORC2-mediated L1 silencing (Fig. 4f). Although observed effects on active host genes are only modulatory, they occur to various extents at hundreds of human genes, illustrating how TE activity can rewire host gene expression patterns.

Online Content Methods, along with any additional Extended Data display items and Source Data, are available in the online version of the paper; references unique to these sections appear only in the online paper.

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Supplementary Information is available in the online version of the paper.

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