Genomic DNA was isolated using PureLink Genomic DNA Mini Kit (K182001, Life Technologies) with RNase A digestion to remove contaminant RNA, according to the manufacturer's instructions. 300 ng genomic DNA per sample was digested with 50 units PspGI (R0611S, New England Biolabs) in 1x smart buffer (NEB) at 75 °C for 1hr, to cut uniquely at the intron of the GFP cassette. The reaction mixture was then used in qPCR experiments with primers flanking the intron in the GFP cassette (**Table S4**). Due to the PspGI digestion, the original unspliced L1-GFP reporter will not be amplified by PCR. Only newly integrated GFP cassettes, where the intron was removed during the retrotransposition process, can be PCR amplified. qPCR runs and analysis were performed on the Light Cycler 480II machine (Roche).

Northern Blotting. Northern blotting was conducted as previously described[38]. Briefly, 15 μg of total RNA from K562 cells or H9 ESC cells was separated on the 0.7% formaldehyde agarose gel, capillary transferred overnight in 20x SSC to the Hybond N membrane (GE Healthcare), crosslinked with a Stratalinker (Stratagene), and hybridized with ^{32}P-labeled single-stranded DNA probes (10^6 cpm/ml) in ULTRAhyb-Oligo Hybridization Buffer (AM8663, Life Technologies) following the manufacturer's instructions. Blots were washed two times with wash buffer (2X SSC, 0.5%SDS), and then exposed to film overnight to several days at −80 °C with an intensifying screen. The sequence of oligonucleotide probes is in **Table S3**.

Single molecule FISH. Single molecule FISH (smFISH) assays were performed following the affymetrix Quantigene ViewRNA ISH Cell Assay user manual. 2.5-5 million live K562 cells were fixed within 4% formaldehyde in 1x PBS for 60 mins at RT, resuspended in 1x PBS, pipetted onto poly-L-lysine coated glass cover slip (∼20,000 total cells/spot; spread out with a pipette tip), and baked in dry oven at 50±1 °C for 30 minutes to fix the cells onto the glass slip, followed by digestion with Protease QS (1:4000) in 1x PBS for 10 minutes at RT. Cells were hybridized with smFISH probes, designed to target beta actin mRNA (FITC channel) and the L1-GFP reporter mRNA (Cy3 channel), DAPI stained for 5 mins, and mounted with Prolong Gold Antifade Reagent (10 ml/sample). Images were taken by spinning disk confocal microscope equipped with 60x 1.27NA water immersion objective with an effective pixel size of 108x108 nm. Specifically, for each field of view, a z-series of 8 μm is taken with 0.5 μm/z-step for all 3 channels. For quantitation, maximum-projected images from the z-series is used and analyzed by a custom-written matlab script. In brief, all images are first subtracted with the background determined with the OTSU method[39] from the log-transformed image after pillbox blurring with a radius of 3 pixels. mRNA puncta are segmented by tophat filter using the background subtracted images and only the ones above 25th percentile intensity of all segmented puncta are taken for downstream analysis. Each punctum is then assigned to the nuclear mask identified by image areas above the previously determined background. For each single cell, the assigned pixel area of L1-GFP mRNA is then normalized to the assigned pixel area of beta-actin mRNA per cell.

RNA-seq. Two independent biological replicates of K562 cells in culture were extracted to isolate DNA-free total RNA sample, using the RNeasy kit (74104, Qiagen) combined with the RNase-Free DNase Set (79254, Qiagen). PolyA-selected RNA were isolated using 'Dynabeads mRNA Purification Kit for mRNA Purification from Total RNA preps' (610-06, Life Technologies) following the manuals. 100 ng polyA-selected RNA was fragmented with NEBNext Magnesium RNA Fragmentation Module (E6150S, New England Biolabs), and used for first strand cDNA synthesis with SuperScriptII (18064-014, Invitrogen) and random hexamers, followed by second strand cDNA synthesis with RNAseH (18021-014, Invitrogen) and DNA PolI (18010-025, Invitrogen). The cDNA was purified, quantified, multiplexed and sequenced with 2x 75bp pair-end reads on an Illumina NEXT-seq (Stanford Functional Genomics Facility).

RNA-seq reads were aligned to hg38 reference genome with hisat2 (--no-mixed, --no-discordant) without constraining to known transcriptome. Known (gencode 25) and de-novo transcript coverages were quantified with featureCount. Repeat Masker coverage was quantified with bedtools coverage. Reads mapping to the same repeat family were then tabulated together, since individual read coverage was too low to obtain meaningful results. Differential expression analysis of join gene-repeat data was performed with DESeq2[40].

ChIP-seq. Two replicates of ChIP experiments per sample were performed as previously described[41,42]. Approximately 0.5–1 × 10^7 cells in culture per sample were crosslinked with 1% paraformaldehyde (PFA) for 10 min at room temperature (RT), and quenched by 0.125 M glycine for 10 min at RT. Chromatin was sonicated to an average size of 0.2-0.7 kb using a Covaris (E220 evolution). Sonicated chromatin was incubated with 5-10 μg antibody bound to 100 μl protein G Dynabeads (Invitrogen) and incubated overnight at 4 °C, with 5% kept as input DNA. Chromatin was eluted from Dynabeads after five times wash (50 mM Hepes, 500 mM LiCl, 1 mM EDTA, 1% NP-40, 0.7% Na-deoxycholate), and incubated at 65 °C water bath overnight (12-16 hrs) to reverse crosslinks. ChIP DNA were subject to end repair, A-tailing, adaptor ligation and cleavage with USER enzyme, followed by size selection to 250-500 bp and amplification with NEBNext sequencing primers. Libraries were purified, quantified, multiplexed (with NEBNext Multiplex Oligos for Illumina kit, E7335S) and sequenced with 2x 75 bp pair-end reads on an Illumina NEXT-seq (Stanford Functional Genomics Facility).

ChIP-seq reads were trimmed with cutadapt (-m 50 -q 10) and aligned with bowtie2 (version 2.2.9, --no-mixed --no-discordant --end-to-end -maxins 500) to the hg38 reference genome. ChIP peaks were called with macs2 (version 2.1.1.20160309) callpeak function with broad peak option and human genome effective size using reads form corresponding loss of gene lines as background model. Visualization tracks were generated with bedtools genomecov (-bg -scale) with scaling factor being 10^6/number aligned reads and converted to bigWig with bedGraphToBigWig (Kent tools). BigWigs were plotted with IGV browser. Individual alignments were inspected with IGB browser.

Heatmaps were generated by intersecting bam alignment files with intervals of interest (bedtools v2.25.0), followed by tabulation of the distances of the reads relative to the center of the interval and scaling to account for total aligned read numbers (10^6/number aligned). Heatmaps were plotted using a custom R function. Aggregate plots were generated by averaging rows of the heatmap matrix. For ChIPs in Ctrl and KO K562 clones, ChIP-seq signals in the corresponding KO cells were used as the null reference.

For ChIP-seq repetitive sequence relationship analysis, repeat masker was intersected with ChIP-seq peak calls to classify each masker entry as MPP8 bound, MORC2-bound or unbound. Enriched families of repeats were identified with R fisher.test() followed by FDR correction with qvalue(). Distribution of sizes of occupied vs non-occupied L1 was plotted using R density() with sizes being taken from repeat masker. ks.test() was used to reject null hypothesis that distribution of sizes for bound and unbound L1s is the same. To investigate relationship between L1 age, length and occupancy, logistic regression was performed with R glm() engine.

Quantitative analysis of H3K9me3 changes was performed by first identifying regions of significant enrichment in each sample relative to corresponding input sample (macs2 callpeak), merging the intervals into a common superset. This superset was joined with a decoy randomized set of intervals, twice the size of actual experimental interval set, with the same size distribution (bedtools shuffle). Next the read coverage was determined for each sample (bedtools coverage) and regions with significant change together with fold changes were identified using DESeq2[40]. H3K9me3 regions were classified into bound vs unbound by performing intersect with MORC2 and MPP8 ChIP peak calls.

Data availability. All sequencing data generated in this work has been deposited at GEO under the accession number: GSE95374. H3K4me3 and H3K27ac K562 ChIP-seq datasets in Fig. 3e are from BioProject (accession number PRJEB8620). hESC RNA-seq datasets in Extended Data Fig. 8c are from SRA run entries SRR2043329 and SRR2043330. The complete results of genome-wide screens in K562 and HeLa cells are in Table S1; The complete results of secondary screens in K562 and HeLa cells are in Table S2. The sequences of gRNAs and oligonucleotides used in this work are in Table S3 and Table S4. The uncropped scans with size marker indications are summarized in the Supplementary Figure. All data are available from the corresponding author upon reasonable request.

Code availability. Detailed Data and further code information are available on request from the authors.

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