## EXTENDED EXPERIMENTAL PROCEDURES

### Prediction of coding potential with PhyloCSF

A Multiz alignment of 46 vertebrates aligned to GRCh37/hg19 for *CENPB, JUND, UBC, ERBB2, NEAT1, XIST, and NORAD* (*LINC00657*) in multiple alignment format (MAF) and BED files containing strand-specific genomic coordinates for the exons in each gene were downloaded from the UCSC Table Browser and uploaded to Galaxy (https://usegalaxy.org/) (Blankenberg et al., 2010). These files were used with the 'Stitch MAF blocks' followed by 'Concatenate FASTA alignment by species' functions of Galaxy to generate FASTA alignments for each gene in the 29 mammals specified by the PhyloCSF phylogeny (http://mlin.github.io/PhyloCSF/29mammals.nh.png). PhyloCSF (Lin et al., 2011) was run with the resulting FASTA file using the following parameters: [--orf=ATGStop --frames=3 --removeRefGaps --aa --allScores].

### 3′ RACE

3′ RACE was performed using the GeneRacer kit (Life Technologies) and primers listed in **Table S5**.

### Measurement of *NORAD* expression in knockout cell lines

qRT-PCR (**Figure S1D**) and RNA-seq (**Table S3**) were used to assess *NORAD* expression after genome editing. Notably, these measurements revealed greatly reduced but detectable *NORAD* expression in knockout clones. Two lines of evidence indicate that this residual expression is not an artifact due to detection of expression of the *NORAD*-related sequences present in the human genome but rather results from leaky transcription through the STOP cassette inserted in the *NORAD* gene. First, the Taqman assay used to detect *NORAD* (**Figure S1D**) utilizes a minor groove binding (MGB) probe that is sensitive to single nucleotide mismatches and was designed to recognize only *NORAD* and none of the related sequences encoded elsewhere in the genome. Furthermore, we generated HCT116 cells with complete homozygous deletion of the entire *NORAD* gene using CRISPR/Cas9 and two flanking sgRNAs. Using the aforementioned Taqman assay, *NORAD* expression was undetectable in these cells (data not shown). These results strongly suggest that the transcriptional stop cassette does not completely prevent *NORAD* expression, perhaps due to a particularly strong promoter driving transcription of this lncRNA.

**Southern blotting**

Genomic DNA was isolated using DNeasy (Qiagen) and digested with SphI. 10 μg of digested DNA was electrophoresed on a 0.7% agarose gel and transferred to Hybond N+ membrane (Amersham). The probe was generated by purifying the 483 bp BsaI-HindIII fragment of Lox-Stop-Lox TOPO (Addgene plasmid #11584) (Jackson et al., 2001) and radiolabeled using the Random Primed DNA Labeling Kit (Roche).

**Flow cytometry**

Assessment of DNA content by propidium iodide staining and flow cytometry was performed as previously described (Hwang et al., 2007). For phospho-Histone H3 (Ser10) staining, trypsinized cells were fixed in 4% formaldehyde for 10 min, washed with PBS, and incubated with 100 μL incubation buffer (1% BSA and 0.1% Triton X-100 in PBS) with antibody (9701, Cell Signaling) diluted at 1:50 followed by staining with goat anti-rabbit antibody conjugated to AlexaFluor 488 (Life Technologies).

**Time-lapse imaging**

Cells were grown on NUNC chambered coverglasses (Thermo). To visualize DNA in HCT116 cells, a cell permeable Hoechst dye (33342; Invitrogen) was used at 25-50 ng/mL. Time-lapse fluorescence images were collected every 5 minutes for 24-48 hours using a Leica inverted microscope equipped with an environmental chamber that controls temperature and $CO_2$, a 63X oil-objective, an Evolve 512 Delta EMCCD camera, and Metamorph software (MDS Analytical Technologies).

**Subcellular fractionation**

Cytoplasmic, nuclear soluble, and chromatin-associated fractions were generated as described previously (Cabianca et al., 2012). Briefly, cells were harvested by trypsinization and lysed in RLN1 solution (50 mM Tris-HCl pH 8.0, 140 mM NaCl, 1.5 mM $MgCl_2$, 0.5% NP-40, 2 mM VRC) in ice for 5 min. After centrifugation, the supernatant was collected as the cytoplasmic fraction while the pellet was further extracted with RLN2 solution (50 mM Tris-HCl pH 8.0, 500 mM NaCl, 1.5 mM $MgCl_2$, 0.5% NP-40, 2mM VRC). Further centrifugation yielded the nuclear-soluble fraction as supernatant and chromatin-associated fraction as pellet. RNA was extracted from fractions with Trizol (Life Technologies).

**RNA FISH**

A Stellaris single molecule FISH probe for *NORAD* was designed using the Stellaris Probe designer (https://www.biosearchtech.com/stellarisdesigner/). Each probe consists of a pool of 48 oligonucleotides, each labeled with CAL Fluor Red 610. Cells were grown on Nunc Lab-Tek II CC2 chambered slides (Thermo) and fixed with 4% formaldehyde for 10 min. Fixed cells were permeabilized in 70% EtOH for 1 hour and dehydrated for 2 min each in 70%, 80%, 95%, and 100% EtOH, then air-dried. Slides were washed in PBS with 0.1% Tween 20 and hybridized at 37°C overnight in 100 μL hybridization buffer (100 mg/mL dextran sulfate, 10% formamide in 2X SSC) containing 125 nM probe per each 22 mm x 22 mm surface under a coverglass sealed with rubber cement. Slides were washed with 10% formamide in 2X SSC and mounted with ProLong Gold Antifade with DAPI (Molecular probes).

***NORAD* affinity purification and mass spectrometry**

*NORAD* fragments were amplified with primers containing T7 and SP6 promoter sequences (**Table S5**) and used as templates for the MEGAscript T7/SP6 Transcription Kit (Ambion) with the Biotin RNA labeling mix (Roche). *In vitro* transcribed RNA was treated with DNase I and purified with the RNeasy kit (Qiagen). 30 pmol purified biotinylated RNA was heated to 90°C in 60 μL RNA structure buffer (10 μM Tris-Cl pH 7.0, 0.1 M KCl, 10 mM $MgCl_2$) for 2 minutes then put on ice for 2 minutes. $2\times10^7$ cells were harvested by scraping and snap-frozen before resuspension in 1.2 mL lysis buffer [150 mM NaCl, 50 mM Tris-Cl pH 7.5, 0.5% Triton X-100, 1mM PMSF, 1x protease inhibitor cocktail (Roche), and 100 U/ml of SUPERaseIN (Ambion)]. Lysates were sonicated using a Bioruptor (Diagenode) for 10 min with 30 sec on/off cycles and pre-cleared with 50 μL washed streptavidin C1 Dynabeads (Invitrogen) at 4°C for 1 hour. 30 pmol biotinylated RNA was then added to pre-cleared lysates and rotated at 4°C for 2 hours, followed by addition of 50 μL streptavidin C1 Dynabeads and further rotation for 1 hour. Beads were washed 6 times with lysis buffer at 4°C and proteins were eluted by incubating in RNase A buffer (50 mM Tris-Cl pH 7.5, 150 mM NaCl, 100 μg/mL RNase A) for 35 minutes at 37°C. Eluted proteins were subjected to label-free quantification using mass spectrometry and SINQ spectral index analysis (Trudgian et al., 2011) at the UT Southwestern Proteomics core. Proteins detectable in at least 1 sense *NORAD* fragment pull-down with ≥5 spectral counts were included in subsequent analyses (**Table S1**).

**Immunoprecipitation and antibodies**

For PUM immunoprecipitation, $1\times10^7$ cells were resuspended in 1 mL Polysome Lysis Buffer (PLB; 15 mM Tris-Cl pH 7.4, 300 mM NaCl, 15 mM $MgCl_2$, 1% Triton X-100, 1 mM DTT, 100 U/mL SUPERase-IN, 1 mM PMSF, 1X Roche protease inhibitor cocktail) and incubated on ice for 30 min. Lysates were pre-cleared with washed Protein G magnetic beads (Novex) at 4°C for 30 minutes. 10 mg of PUM1 antibody (sc-135049, Santa Cruz), PUM2 antibody (sc-31535, Santa Cruz), rabbit IgG (sc-2027, Santa Cruz), or goat IgG (sc-2028, Santa Cruz) were incubated with 200 mL Protein G magnetic beads in PBS with 0.02% Tween-20 for 30 min at room temperature and added to the pre-cleared lysates, followed by rotation at 4°C for 4 hours and 3 washes in PLB on ice. 10% of beads were resuspended in Laemmli buffer for western blotting and RNA was isolated from the remaining beads using Trizol. Antibodies used for western blotting were PUM1 (ab92545, Abcam), PUM2 (ab92390, Abcam), α-Tubulin (T9026, Sigma), and GAPDH (2118, Cell Signaling).

**Recombinant PUMILIO protein purification**

Human *PUM1* and *PUM2* UltimateORF clones (Life Technologies) were subcloned into destination vector pDEST17 (Life Technologies) using Gateway LR Clonase II Enzyme mix (Life Technologies) for expression of 6Xhistidine tagged-recombinant proteins. Plasmids were transformed into Rosetta 2(DE3)pLysS competent cells (Novagen) and recombinant proteins were induced with 0.2 mM IPTG at 20°C. Bacteria were lysed in 8 M urea lysis buffer (100 mM $NaH_2PO_4$, 10 mM Tris-Cl, 8 M urea, pH 8.0) and bound proteins were recovered on Ni-NTA agarose resin, washed with lysis buffer at pH 6.3, and eluted with 250 mM imidazole at pH 4.5. The concentration of purified proteins was determined by electrophoresis alongside a serial dilution of BSA standards (Pierce) with coomassie staining.

**PAR-CLIP**

PAR-CLIP was performed essentially as described in (Spitzer et al., 2014). Briefly, HCT116 cells and isogenic *NORAD*$^{-/-}$ cells were grown to ~80% confluence at which point 4-thiouridine (Sigma) was added to the media at final concentration of 100 μM. After 18 hours, 4-thiouridine-labeled cells were washed with cold PBS and crosslinked using 365 nm UV with 150 mJ/cm$^2$ total energy in a Spectrolinker XL-1500 (Spectroline). A total of ~720 million cells (36 150 mm dishes) per CLIP condition were collected and resuspended in NP-40 lysis buffer (50 mM

HEPES-KOH, pH 7.5, 150 mM KCl, 2mM EDTA-NaOH, pH 8.0, 1 mM NaF, 0.5% NP-40 substitute, 0.5 mM DTT, and Complete EDTA-free protease inhibitor cocktail). After centrifugation, the soluble fraction was filtered through a 5 μm syringe filter and incubated with 1 U/μL RNase T1 at 22ºC for 15 min. 100 μg PUM2 antibody (K-14, sc-31535, Santa Cruz) was conjugated to Protein G magnetic beads and incubated with RNase-treated lysate at 4ºC for 4 hours. Bead-bound PUM2 RNP complexes were washed with IP wash buffer (50 mM HEPES-KOH, pH 7.5, 300 mM KCl, 0.05% NP-40 substitute, 0.5 mM DTT and Complete EDTA-free protease inhibitor cocktail) followed by an additional RNase T1 treatment (1 U/μL at 22ºC for 15 min). Beads were further washed with high-salt wash buffer (50 mM HEPES-KOH, pH 7.5, 500 mM KCl, 0.05% NP-40 substitute, 0.5 mM DTT and Complete EDTA-free protease inhibitor cocktail) and the 5′ ends of PUM2 bound RNAs were labeled with $^{32}$P using calf intestinal alkaline phosphatase followed by T4 PNK and [γ-32P]-ATP. 100 μM unlabeled ATP was added after radiolabeling to ensure all RNA species were 5′-phosphorylated. Labeled RNP complexes were eluted from beads by boiling in 1X SDS-PAGE loading buffer (62.5 mM Tris HCl pH 6.8, 1.5% SDS, 8.3% Glycerol, 0.005% Bromophenol blue) and resolved on an SDS-PAGE gel. After autoradiography, bands corresponding to the PUM2 RNP size (~120 kDa) were excised and electro-eluted using D-tube dialyzer tubes (Milipore) in MOPS-SDS running buffer. Eluted samples were then digested with 1.2 mg/mL Proteinase K (Sigma) at 55ºC for 30 min. RNA was isolated using phenol/chloroform extraction followed by ethanol precipitation. Sequencing libraries were constructed using the TruSeq Small RNA Library Preparation Kit (Illumina). Sequencing was performed on a NextSeq 500 (Illumina).

Quality assessment of the CLIP-Seq data was done using NGS-QC-Toolkit (Patel and Jain, 2012). Reads with mean phred quality scores of less than 20 were removed from further analysis. Cutadapt (v1.2.1) (Martin, 2011) was used to remove the sequencing adapters using default settings and all reads 15 nt or longer were aligned to repeat masked *NORAD* and the human transcriptome (Ensembl GRCh37.75) in two-steps: First, all reads were aligned to *NORAD* using Bowtie (v1.0.0) (Langmead et al., 2009), requiring unique mapping within *NORAD* and allowing up to 1 mismatch (-v 1 -m 1). Then the rest of the reads were aligned to the transcriptome using Bowtie with the settings (-a -m 1). CLIP crosslinking sites were identified as follows: 1) All transcriptome coordinates were converted to genomic coordinates and all reads with unique genomic location were kept; 2) PCR duplicates were removed; 3)

Reads with at least 1 nt overlap were clustered; 4) All clusters with at least 5 reads and at least 1 T to C mutation were defined as CLIP clusters.

**PUMILIO overexpression**

Human *PUM1* and *PUM2* UltimateORF clones (Life technologies), or eGFP as a negative control, were subcloned into pLX302 (Addgene plasmid #25896) (Yang et al., 2011) using Gateway LR Clonase II Enzyme mix (Invitrogen). The resulting lentiviral backbones were packaged in HEK293T cells by co-transfection with psPAX2 and pMD2.G (Addgene plasmids #12260 and #12259). Viral supernatants were passed through a 0.45 micron filter and used to transduce HCT116 cells in the presence of 8 μg/mL polybrene (EMD Milipore). Beginning 48 hours after transduction, cells were selected with 1 μg/mL puromycin for at least 7 days and single cell-derived clones were screened for PUM expression by western blot.

**RNA-seq and analysis**

RNA-seq libraries were prepared using the TruSeq Stranded Total RNA with Ribo-Zero Human/Mouse/Rat Sample Preparation kit (Illumina) and sequenced using the 100 bp paired-end protocol on an Illumina HiSeq 2000 in the McDermott Center Next Generation Sequencing Core at UT Southwestern. For comparing *NORAD*$^{+/+}$ and *NORAD*$^{-/-}$ HCT116 cells, 3 biological replicates per genotype were sequenced with an average paired-read depth of $52\times10^6$. For PUM overexpression experiments, 3 replicates of GFP-expressing HCT116 cells (negative control) and 2 independent PUM1- or PUM2-overexpressing clones (2 replicates each) were sequenced. An average of $27\times10^6$ paired-reads were generated per sample. Quality assessment of the RNA-seq data was performed with NGS-QC-Toolkit (Patel and Jain, 2012). Reads with mean Phred quality scores of less than 20 were removed from further analysis. Filtered reads were then aligned to the human reference genome (hg19) using Tophat2 (v2.0.10) (Kim et al., 2013) with library type setting 'fr-firststranded' and other parameters set to default. Differential gene expression analysis was performed using the R package edgeR (v1.10.1) (Robinson et al., 2010) following a published protocol (Anders et al., 2013). Gene ontology analysis was performed using DAVID (http://david.abcc.ncifcrf.gov) (Huang et al., 2007).

Notably, expression of several Y-linked genes was detected by RNA-seq in parental *NORAD*$^{+/+}$ HCT116 cells but not in derivative *NORAD*$^{-/-}$ cells (**Table S3**). This phenomenon is most likely

due to the fact that approximately 10% of cells in the parental HCT116 population contain a Y chromosome (http://physics.cancer.gov/docs/bioresource/colorectal/NCI-PBCF-CCL247_HCT116_SOP-508.pdf). Because *NORAD*$^{-/-}$ cells are clonal derivatives of the HCT116 population, they are unlikely to have originated from a cell with a Y chromosome, thereby resulting in apparent loss of expression of Y-encoded genes.

**Generation of *PUM1* and *PUM2* knockout cells**

*PUM1*$^{-/-}$ and *PUM2*$^{-/-}$ cells were generated using the CRISPR/Cas9 system to introduce frameshift mutations in exons upstream of the sequence encoding PUMILIO homology domains (PUM-HD), which are essential for target binding. To generate *PUM1* and *PUM2* individual knockouts, single guide RNAs (sgRNAs) targeting exon 7 for *PUM1* and exon 8 for *PUM2* were designed (**Table S5**) and cloned into pX459 (Addgene plasmid, #48139) followed by transfection into HCT116 and puromycin selection. Single cell clones were screened by western blotting using PUM antibodies (Abcam ab92545 for PUM1 and ab92390 for PUM2) and validated by sequencing of mutant alleles after amplification and TA cloning of CRISPR/Cas9 target sites, using primer pairs provided in **Table S5**. To generate *PUM1*$^{-/-}$; *PUM2*$^{-/-}$ double knockout cells, pX458 (Addgene plasmid, #48138) expressing the sgRNA used for single *PUM1* knockout was transfected into *PUM2*$^{-/-}$ cells followed by FACS sorting of GFP$^{+}$ cells and single cell cloning. Screening of double knockout cells was performed by western and sequencing as described above. Finally, to knockout *NORAD* in *PUM1*$^{-/-}$, *PUM2*$^{-/-}$, and *PUM1*$^{-/-}$; *PUM2*$^{-/-}$ cells, TALEN-mediated homologous recombination (HR) was used as described in EXPERIMENTAL PROCEDURES using a modified lox-STOP-lox cassette carrying a hygromycin resistance cassette instead of a puromycin resistance cassette.

***PUM1*/*PUM2* knockdown experiments**

ON-TARGETplus siRNAs (GE-Dharmacon) targeting human *PUM1* (9696) and *PUM2* (23369) were purchased from GE Dharmacon and tested to identify those that yielded the most efficient knockdown. Two siRNAs for *PUM1* and two siRNAs for *PUM2* were selected (target sequences provided in **Table S5**). HCT116 cells were transfected once per day for 3 consecutive days. 5 days after the first transfection, cells were plated on chambered coverglasses and mitoses were recorded by time-lapse imaging as described above.

**Table S4. PUM2 target genes that are downregulated in *NORAD*$^{-/-}$ cells and required for genomic stability, Related to Figure 6.**

| Gene | Category | Notes | References |
|---|---|---|---|
| ESCO2 | Cohesin | Cohesin acetyltransferase; Esco2 knockout in MEFs causes severe chromosome segregation defects. | (Whelan et al., 2012) |
| SMC1A | Cohesin | Component of the cohesin complex; SMC1A knockdown in HCT116 causes CIN. | (Barber et al., 2008) |
| SMC3 | Cohesin | Component of the cohesin complex; SMC3 knockdown in HCT116 causes CIN. | (Barber et al., 2008) |
| CENPJ | Centromere | Centromere protein; Cenpj haploinsufficiency in MEFs causes genomic instability. | (McIntyre et al., 2012) |
| EXO1 | DNA repair | Exonuclease; Exo1 deficiency causes chromosomal aberrations in MEFs. | (Schaetzlein et al., 2013) |
| RBMX | DNA repair | RNA binding protein; RBMX knockdown causes premature chromatid separation and aberrant mitosis; RBMX is involved in DNA repair. | (Adamson et al., 2012; Matsunaga et al., 2012) |
| PARP2 | DNA repair | Poly(ADP-ribose) polymerase; Key DNA repair factor; Parp2 knockout in MEFs causes chromosome mis-segregation upon treatment with an alkylating agent. | (De Vos et al., 2012; Menissier de Murcia et al., 2003) |
| NET1 | DNA repair | Guanine nucleotide exchange factor; NET1 depletion results in aberrant chromosome congression and separation. | (Menon et al., 2013) |
| PARP1 | DNA repair | Poly(ADP-ribose) polymerase; Key DNA repair factor; Parp1 knockout in MEFs causes chromosomal instability. | (De Vos et al., 2012; Samper et al., 2001) |
| RBBP8 | DNA repair | Retinoblastoma binding protein (also known as CTIP); RBBP8 is important for DNA double strand break repair and homologous recombination; RBBP8 knockdown causes genomic instability. | (Terasawa et al., 2014; Wang et al., 2014) |
| BARD1 | DNA repair | BRCA1 associated protein; Bard1-/-;p53-/- mouse embryos display chromosomal abnormalities; reconstitution of BARD1 in Bard1-/- cancer cells reduces chromosomal aberrations. | (Laufer et al., 2007; McCarthy et al., 2003) |
| MCM8 | Replication | Minichromosome maintenance complex component; Mcm8 knockout causes genomic instability in MEFs. | (Lutzmann et al., 2012) |
| WDHD1 | Replication | Also known as CTF4 - Chromosome transmission fidelity 4; CTF4 coordinates DNA unwinding and polymerase activity during replication. | (Kang et al., 2013) |
| MCM4 | Replication | Minichromosome maintenance complex component; Hypomorphic Mcm4 allele causes genomic instability in mice. | (Shima et al., 2007) |
| MASTL | Mitosis | Microtubule-associated serine/threonine kinase-like; MASTL knockdown causes mitotic defects and chromosomal abnormalities. | (Burgess et al., 2010; Voets and Wolthuis, 2010) |
| PRC1 | Mitosis | Protein regulator of cytokinesis; PRC1 is required for cytokinesis and is involved in proper chromosome segregation. | (Jiang et al., 1998; Liu et al., 2009) |
| LMNB2 | Mitosis | Nuclear lamin; LMNB2 knockdown in HCT116 causes CIN; LMNB2 is downregulated in CIN-type colon cancer cell lines. | (Kuga et al., 2014) |
| LIN9 | Other | Subunit of the DREAM complex; Lin9 knockout causes chromosomal instability in MEFs. | (Hauser et al., 2012) |
| SLBP | Other | Stem-loop binding protein; Interacts with Histone mRNA 3' ends; Slbp mutant flies exhibit genomic instability. | (Salzler et al., 2009) |
| HMGB1 | Other | High-mobility group box family member; Hmgb1 knockout in MEFs results in CIN. | (Giavara et al., 2005) |
| DNMT1 | Other | DNA methyltransferase; DNMT1 knockout in HCT116 causes CIN. | (Karpf and Matsui, 2005) |

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