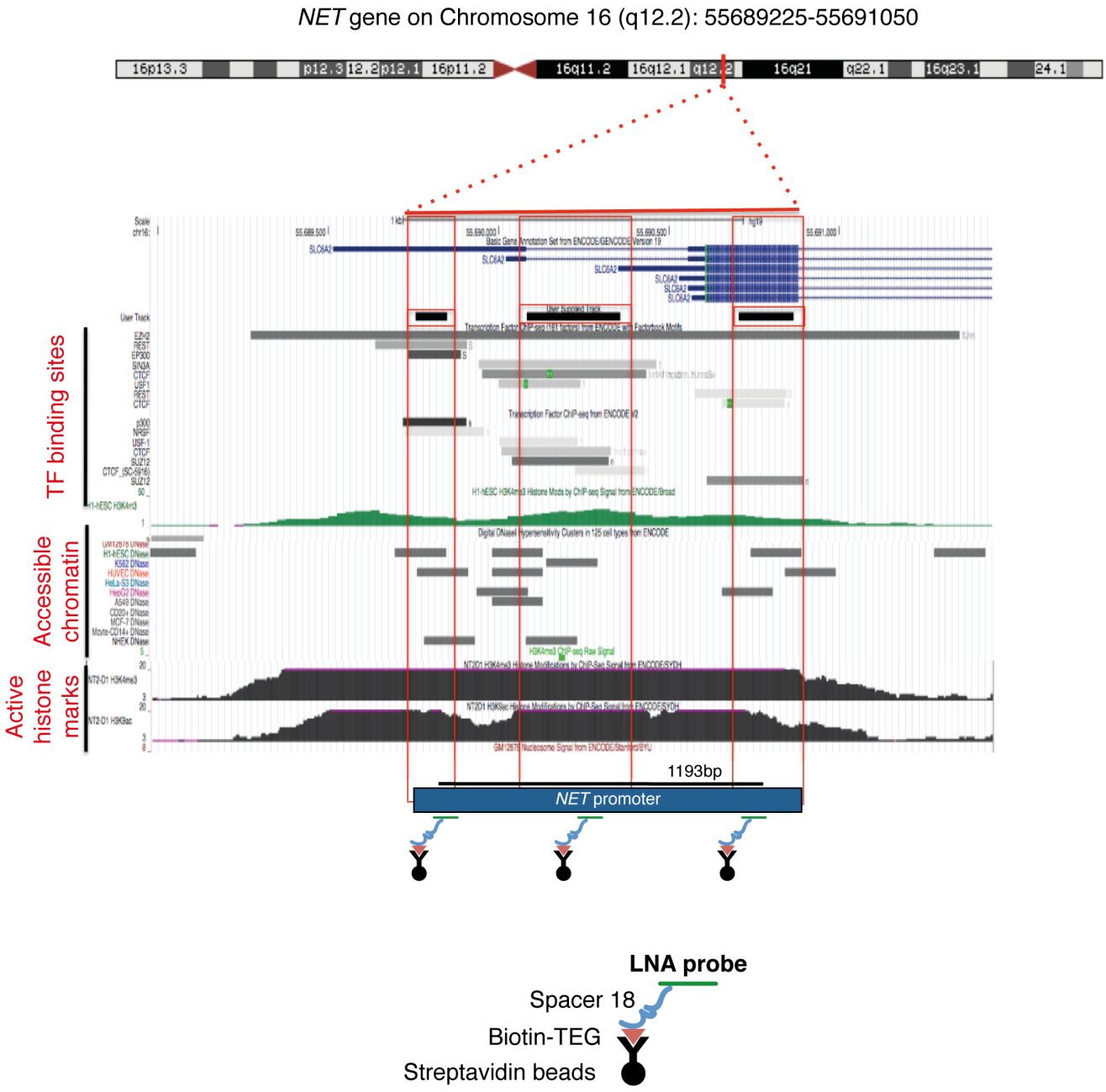
Supplementary Figures

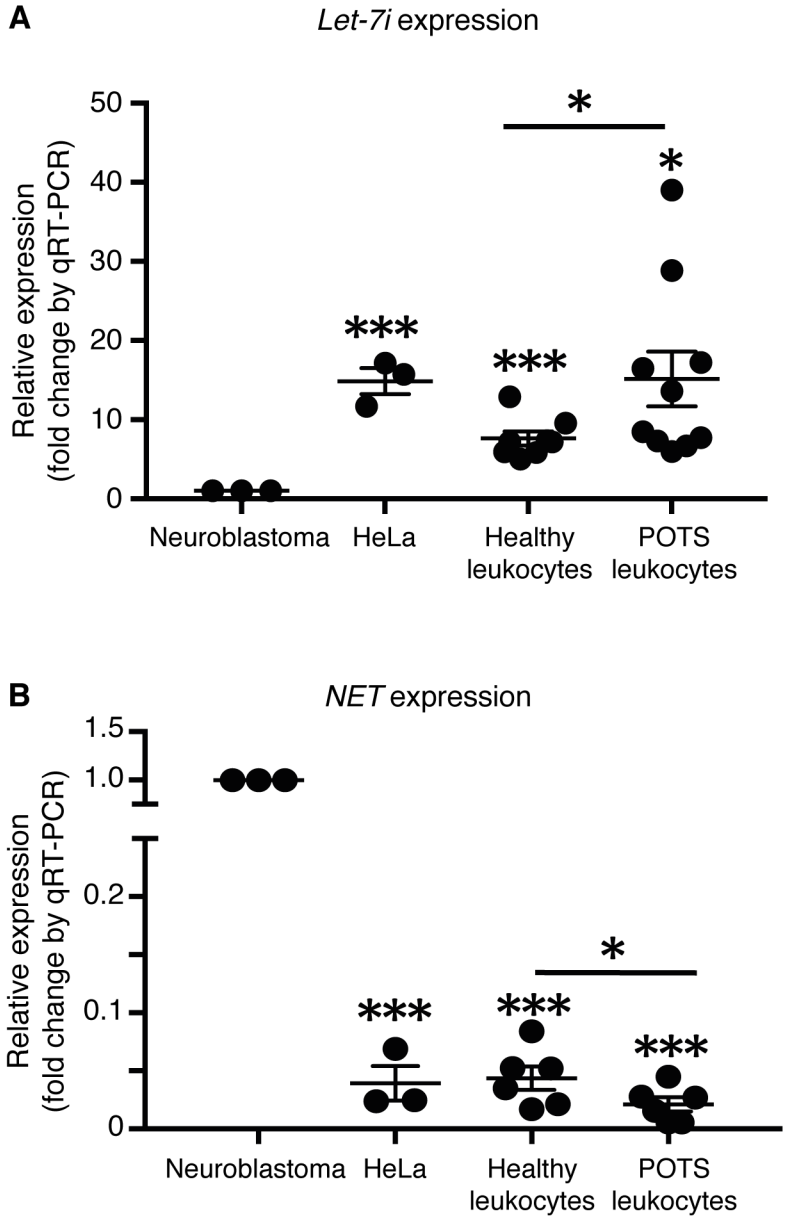
Supplementary figure legends appear on the same page as the corresponding figures.

Supplementary Figure 1



Supplementary Figure 1. Design of *NET* specific LNA probes for RNA of Isolated Chromatin (RICh) assay. Probe design for the *NET* promoter was based on the ENCODE project dataset for transcription factor binding sites, chromatin accessibility and active histone marks such as H3K4me3 and H3K9ac. We used a combination of three specific *NET* probes to capture 1193 bp fragment.

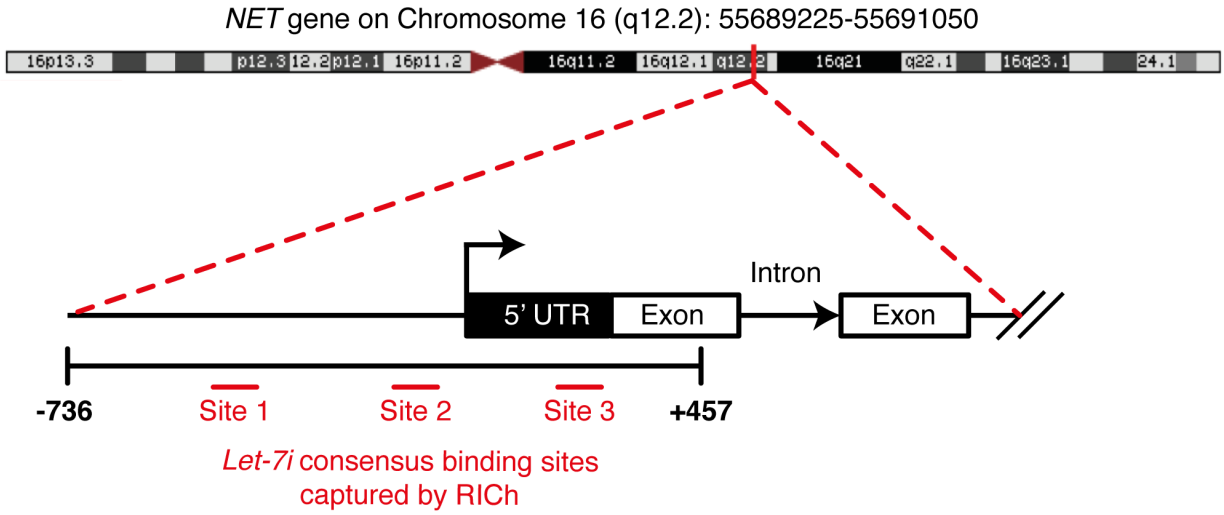
Supplementary Figure 2



Supplementary Figure 2. *NET* and *let-7i* gene expression in primary and non-primary cells.

(**A**) *Let-7i* expression in neuroblastoma cells SK-N-BE (2), HeLa, and leukocytes isolated from healthy and POTS participants; n=9. Relative expression is measured against *U6-2* using qRT-PCR. (**B**) *NET* expression in neuroblastoma cells SK-N-BE (2), HeLa, and leukocytes isolated from healthy and POTS participants; n=9. Relative expression is measured against *ACTB* using qRT-PCR. t test $*P < 0.05$, $**P < 0.01$, error bars represent mean ±SEM.

Supplementary Figure 3

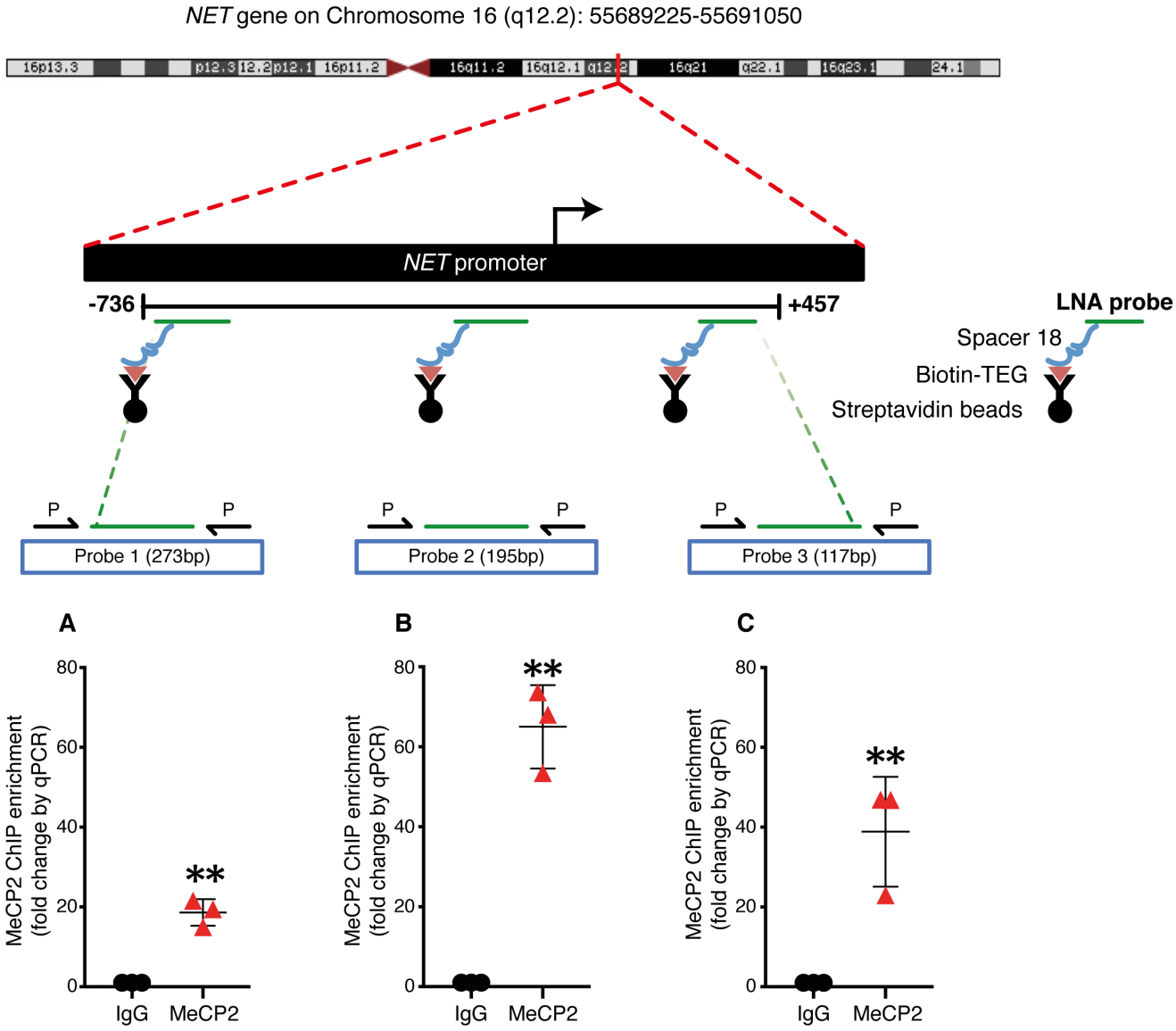


Let-7i binding sites	Sequence homology	Site location	Minimum free energy (mfe) Kcal/mol
Site 1	(*NET*): _ _ G G G C G C A G G C T A C A U T A C C A (*let-7i*): UU G U C G U G U U U G A U G _ _ A U G G A G U	-488 to -468	-27.7
Site 2	(*NET*): T C G G C A C _ _ G C T G C C C T C A G C C T C G (*let-7i*): UU G U C G UGU U U G A UG A_ _ _ _ U G GA G U	-108 to -86	-25.8
Site 3	(*NET*): C G C G G G A C A G G G C T A G G U C T G C C T G G G (*let-7i*): U U G U C G U G U _ U U G A U _ _ _ G AU G GA G U	+165 to +185	-23.9

Supplementary Figure 3. *Let-7i* consensus binding sites at *NET* promoter.

Above schematic of the *NET* promoter (-736 to +457) represents the chromatinized region captured using the RICh-assay. Red regions numbered 1-3 represent the *let-7i* binding sites using the RNA hybrid prediction tool. The table shows *NET* sequence homology with *let-7i* locations and calculated minimum free energy (mfe).

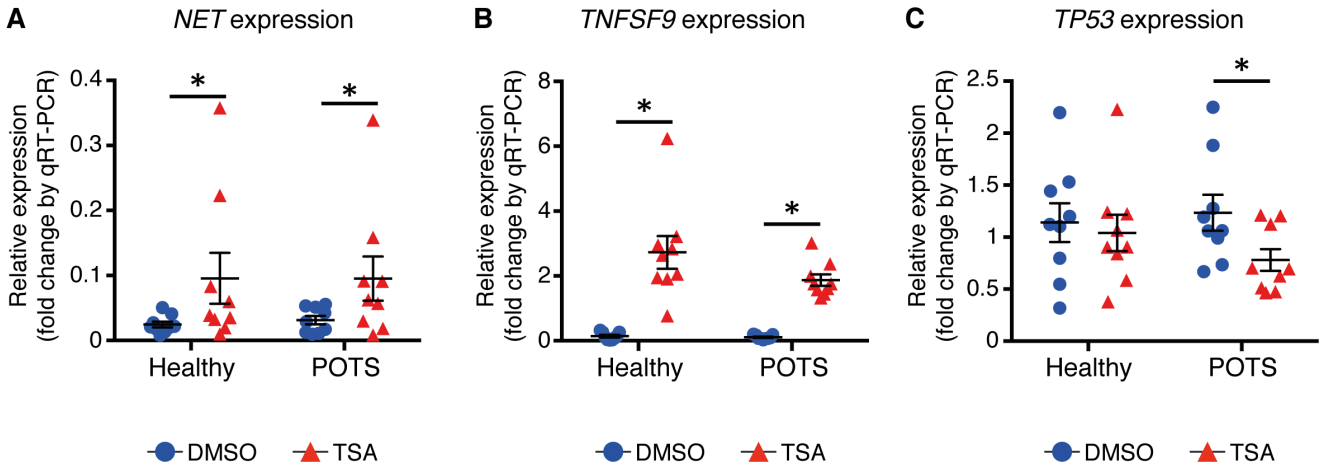
Supplementary Figure 4



Supplementary Figure 4. MeCP2 binds at the LNA probe sequences of the human *NET* promoter.

ChIP assay confirms MeCP2 interacts at the LNA binding sites of the *NET* promoter using primers specific for (A) probe 1, (B) probe 2, and (C) probe 3 in HeLa cells. Primers in schematic are abbreviated as P. n=3. t test **P* <0.05, ***P* <0.01; error bars represent SD.

Supplementary Figure 5.



Supplementary Figure 5. *Ex-vivo* TSA stimulation reactivates *NET* expression in leukocytes derived from healthy and POTS participants.

(**A**) Increased *NET* expression following TSA stimulation of leukocytes derived from healthy and POTS participants. Relative expression is measured against *ACTB* using qRT-PCR. (**B**) Increased *TNFSF9* expression following TSA stimulation of leukocytes derived from healthy and POTS participants. Relative expression is measured against *ACTB* using qRT-PCR. (**C**) *TP53* expression following TSA stimulation of leukocytes derived from healthy and POTS participants. n=9. Relative expression is measured against *ACTB* using qRT-PCR. t test **P* <0.05, ***P* <0.01; error bars represent mean ±SEM**.**

Supplementary Table 1 Small RNA alignment metrics

Sample	**Total reads**	**Mapped**	**Uniquely mapped**
Input 1	710967	87.12%	36566
Input 2	797949	92.22%	291685
Input 3	974187	88.90%	321321
NET-probe 1	192232	84.21%	57030
NET-probe 2	896197	89.32%	202672
NET-probe 3	93600	80.88%	22291
Scramble 1	115790	76.11%	19633
Scramble 2	156110	69.47%	27232
Scramble 3	203515	81.39%	44224

Supplementary Table 2

Gene name	Ensemble ID	Gene biotype	Gene location	Abundance (rank)	Log FC (input)	FDR (input)	Log FC (scr)	FDR (scr)
MIRLET7I	ENSG00000199179	miRNA	chr12:62603686-62603769	Top 10%	2.49	0.000012	4.32	0.00000001
SNORD94	ENSG00000208772	snoRNA	chr2:86135870-86136006	Top 15%	1.30	0.000004	3.21	0.00000152
SNORA46	ENSG00000207493	snoRNA	chr16:58548499-58548633	Top 20%	2.01	0.001550	4.74	0.00000152
SCARNA4	ENSG00000252808	snoRNA	chr1:155895749-155895877	Top 25%	1.82	0.001498	2.90	0.00007441
TUFM	ENSG00000178952	protein coding	chr16:28842411-28846408	Top 25%	2.06	0.001550	2.35	0.00656122

Supplementary Table 2. Summary of RNAs identified by RICh-seq at the *NET* promoter

Chromatin bound RNA transcripts at the *NET* promoter. These transcripts were common in two different methods to analyse RICh-seq data. In method one, the abundance of transcripts using the *NET*-probe is compared to input (total chromatin RNAs). In the second method the abundance of transcripts using the *NET*-probe is compared to scramble (scr) probe. False Discover Rate (FDR) and Log fold changes (Log FC).