

ER-positive breast cancer cells are poised for RET-mediated endocrine resistance

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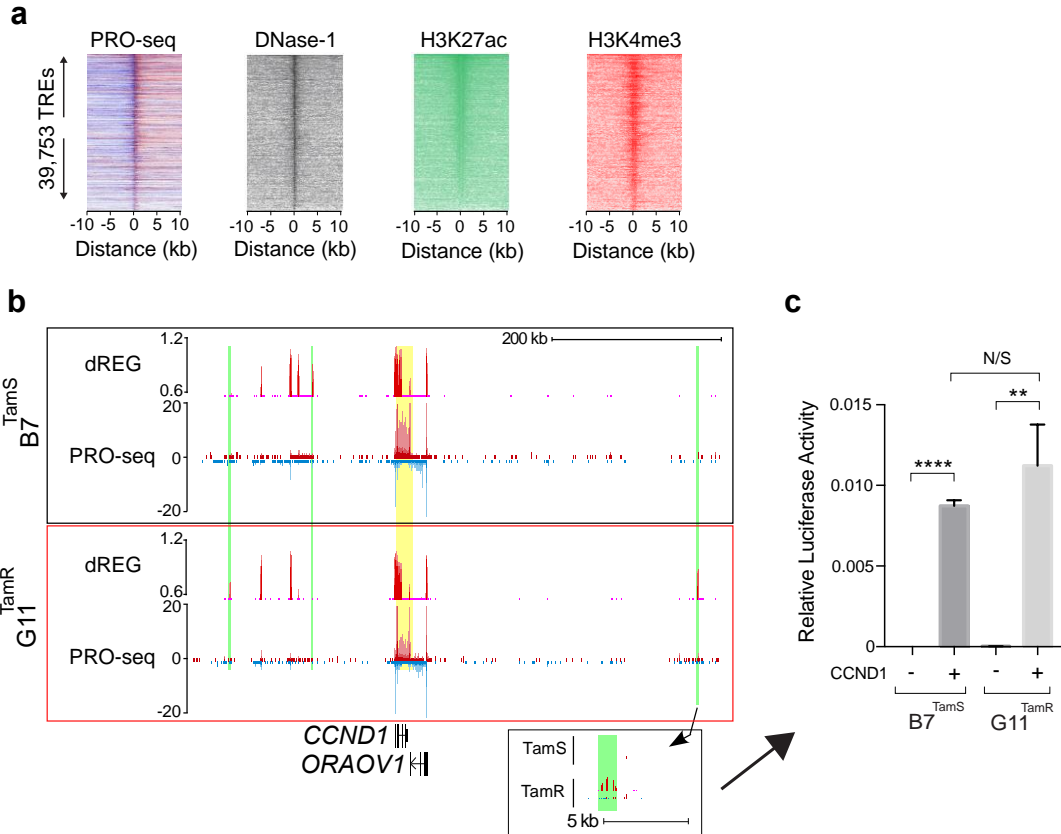
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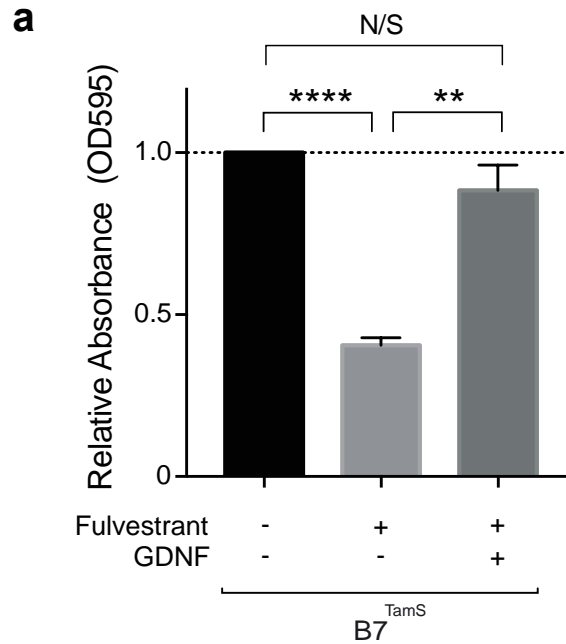
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Cell Clone	Resistance	Treatment	Time	Uniquely mapped reads
B7	TamS	None		21314970
C11	TamS	None		20333086
G11	TamR	None		22161480
H9	TamR	None		23454417
Total:				87,263,953

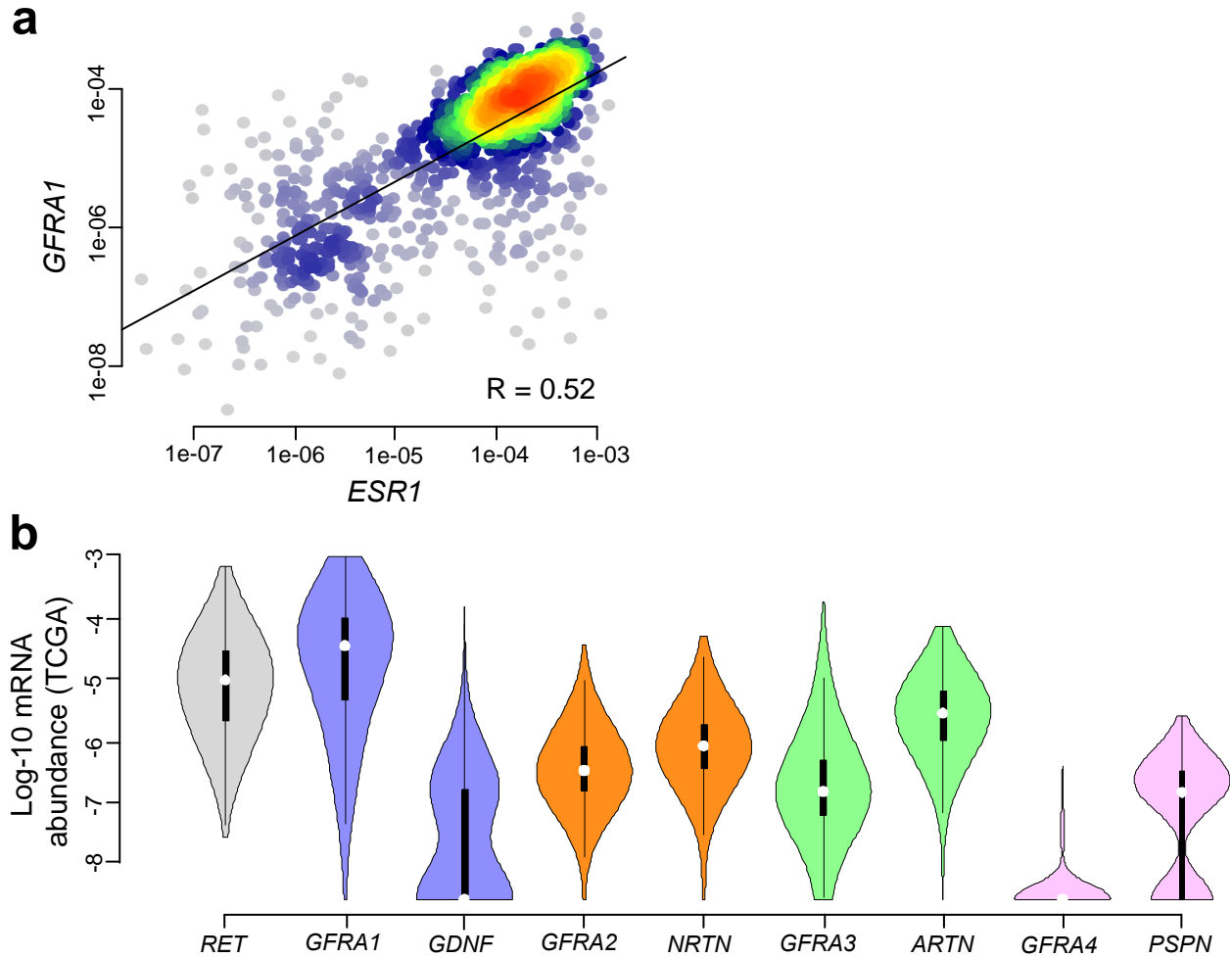
Supplementary Table 1. PRO-seq data collection and sequencing depth. PRO-seq was conducted in the indicated cell clone and biological condition. Raw PRO-seq data were sequenced to a read depth >20 million uniquely mapped reads and aligned using established pipelines.



Supplementary Figure 1. dREG identifies highly enriched active enhancers and promoter makers in MCF-7 cells. (a) Heatmap depicting PRO-seq, DNase-1-seq, H3K27ac, and H3K4me3 near 39,753 transcriptional regulatory elements (TREs) identified using dREG-HD from PRO-seq data (left) in TamS and TamR MCF-7 cells. (b) Transcription and dREG scores in the locus near the *CCND1* gene in B7^{TamS} and G11^{TamR} MCF-7 cells. (c) Luciferase activity in B7^{TamS} and G11^{TamR} MCF-7 cells in the presence of an enhancer located approximately 300kb downstream of *CCND1*. All data normalized to renilla control. Data are represented as mean \pm SEM (n=3). ** p < 0.01, **** p < 0.0001.



Supplementary Figure 2. GDNF induces fulvestrant resistance in TamS cells. (a) Cell viability of B7^{TamS} cells in the presence or absence of 10 ng/ml GDNF and/or 100 mM fulvestrant for 4 days. Data are represented as mean \pm SEM (n=3). ** $p < 0.005$, **** $p < 0.0001$.



Supplementary Figure 3. RET ligand expression is low compared to RET and GFR α 1 receptors. (a) Density scatterplot showing the relationship between *GFRA1* and *ESR1* expression levels in 1,177 primary breast cancer samples in the cancer genome atlas (TCGA). Pearson's $R = 0.52$; $p < 2.2e-16$. (b) Violin plots depicting the absolute normalized expression level of receptor-tyrosine kinase receptors and ligands in 1,177 primary breast cancer samples (TCGA). For each color, the pair of genes represents receptor (left) and ligand (right). Gray represents the *RET* gene which encodes the RET tyrosine kinase receptor required for signal transduction of all four RET ligands.