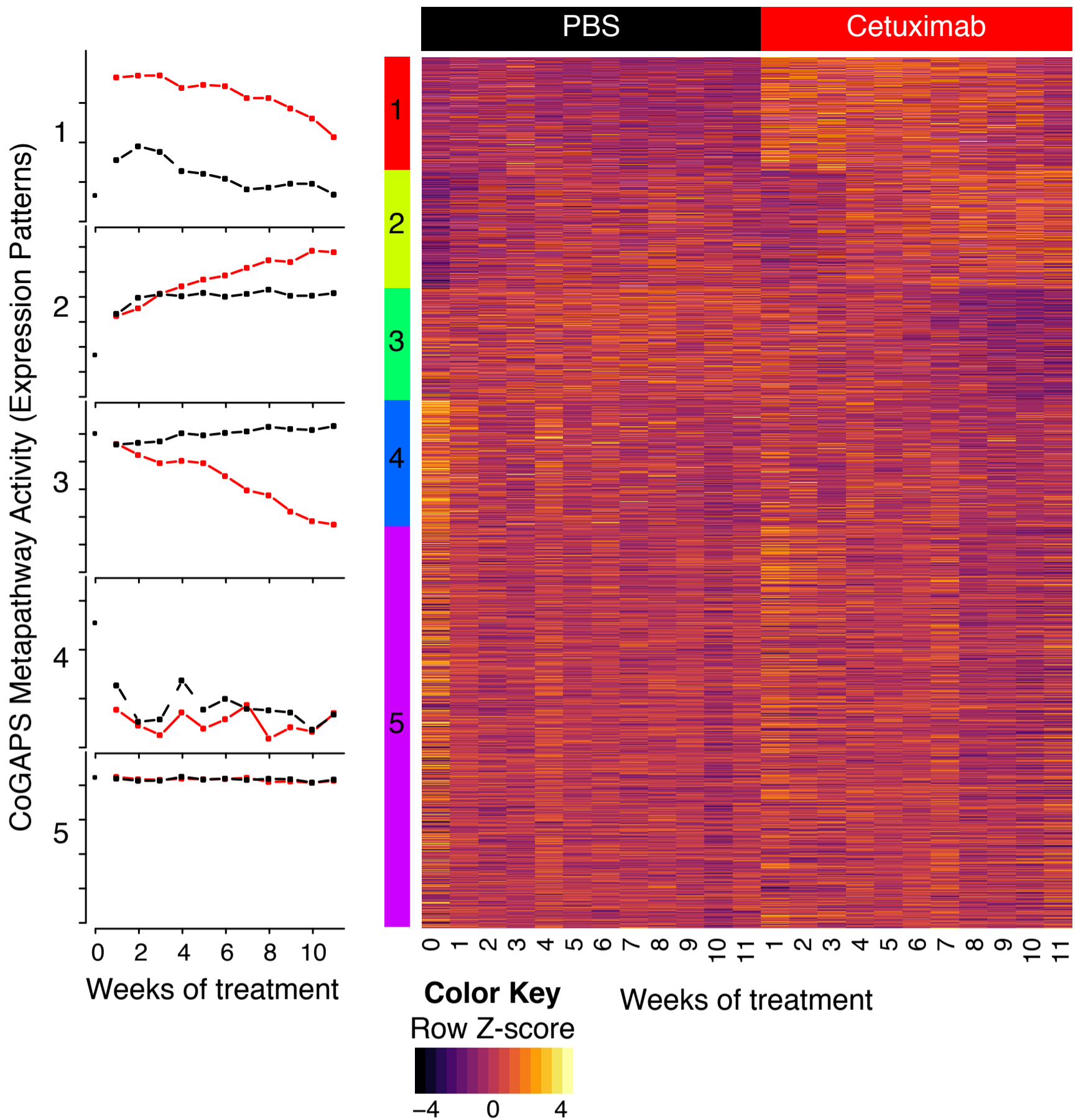
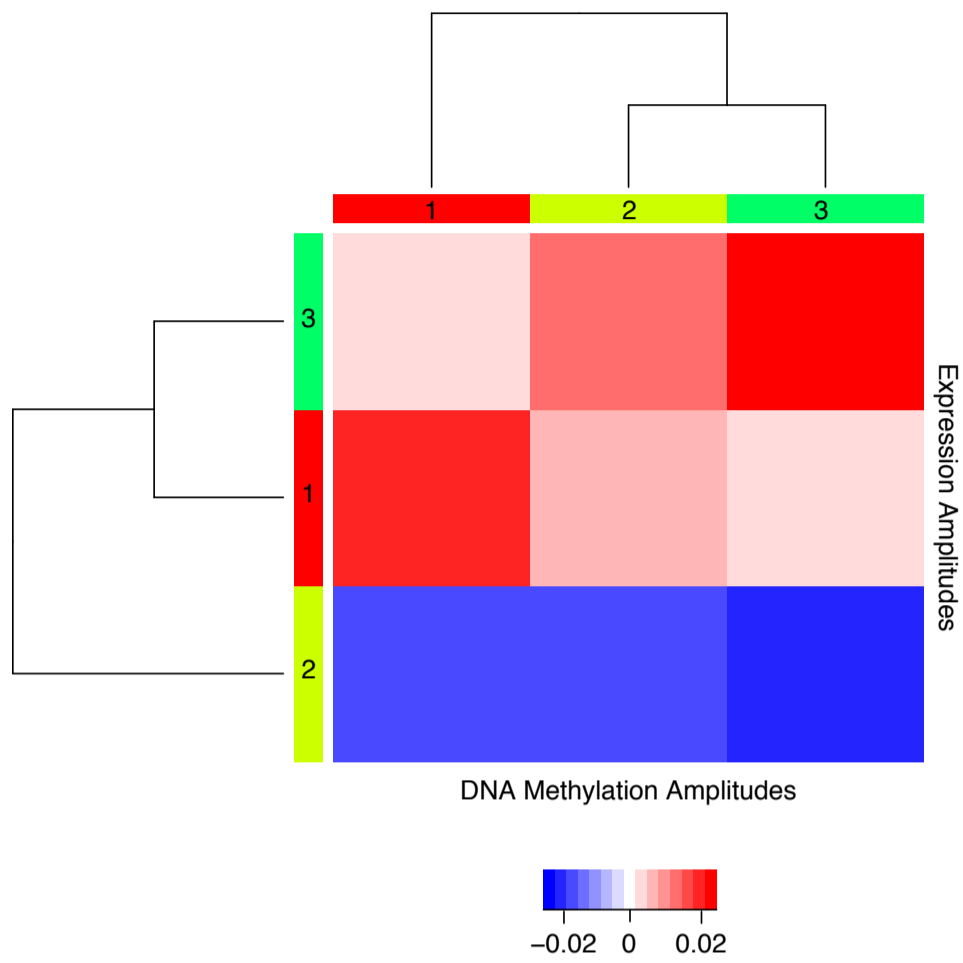


Supplemental Figure 1 - Heatmap and hierarchical clustering of gene expression values in 11 generations of SCC25 cells treated with PBS as control (black columns) and with 100nM of cetuximab (red columns) to acquire resistance.

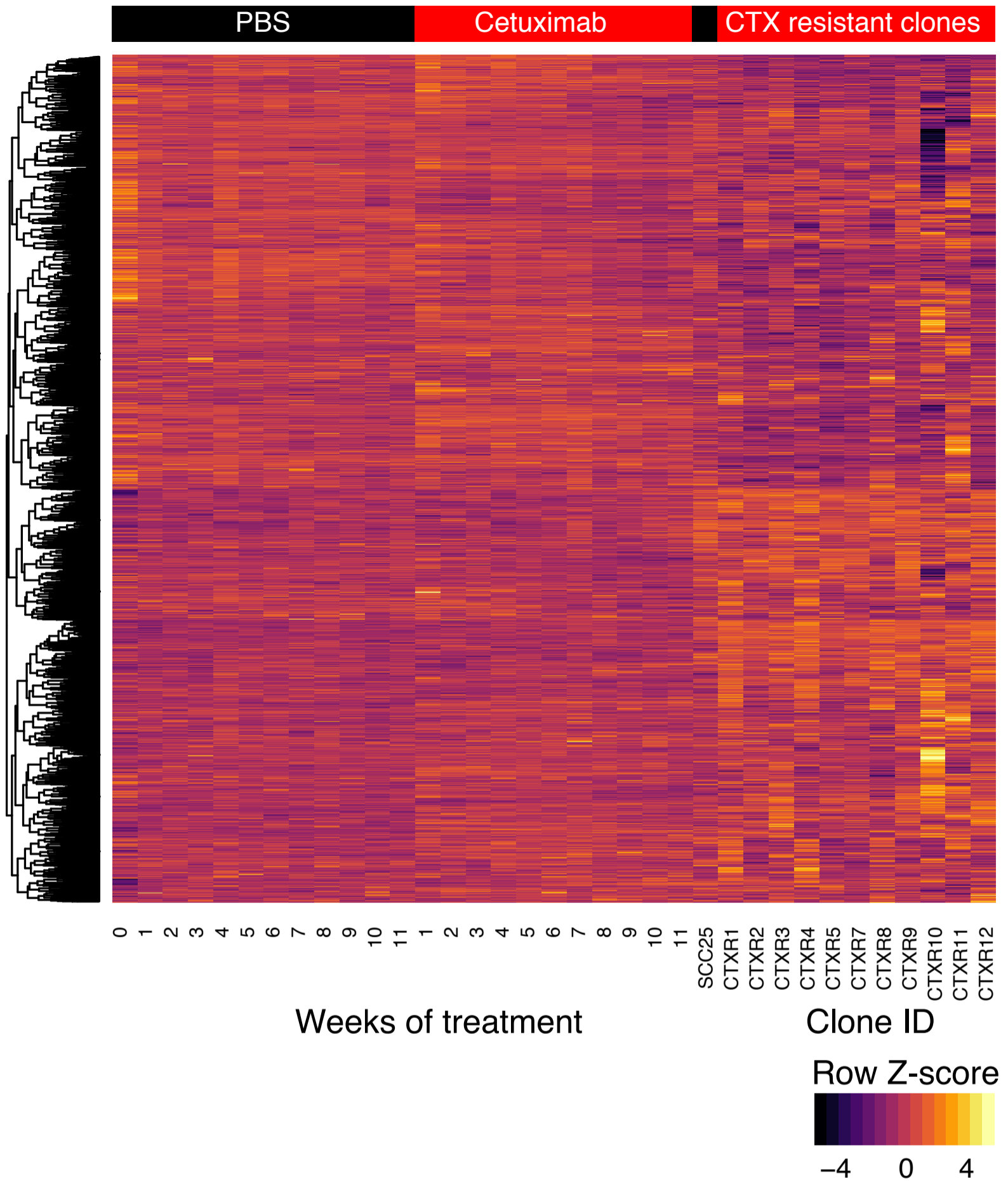


Supplemental Figure 2 - Expected gene expression values for genes in each CoGAPS pattern inferred from gene expression data over generations of PBS control (black lines) or treatment with 100nM of cetuximab (red lines). Patterns include a pattern reflecting technical artifacts between untreated controls at time 0 and subsequent generations (pattern 4) and a flat pattern for highly expressed genes (pattern 5), excluded from analysis in main figures. Heatmap of gene expression values for PatternMarker genes identified for all of these patterns. Rows are colored according to which CoGAPS pattern the PatternMarker statistic assigned each gene, and sorted by the PatternMarker statistic.

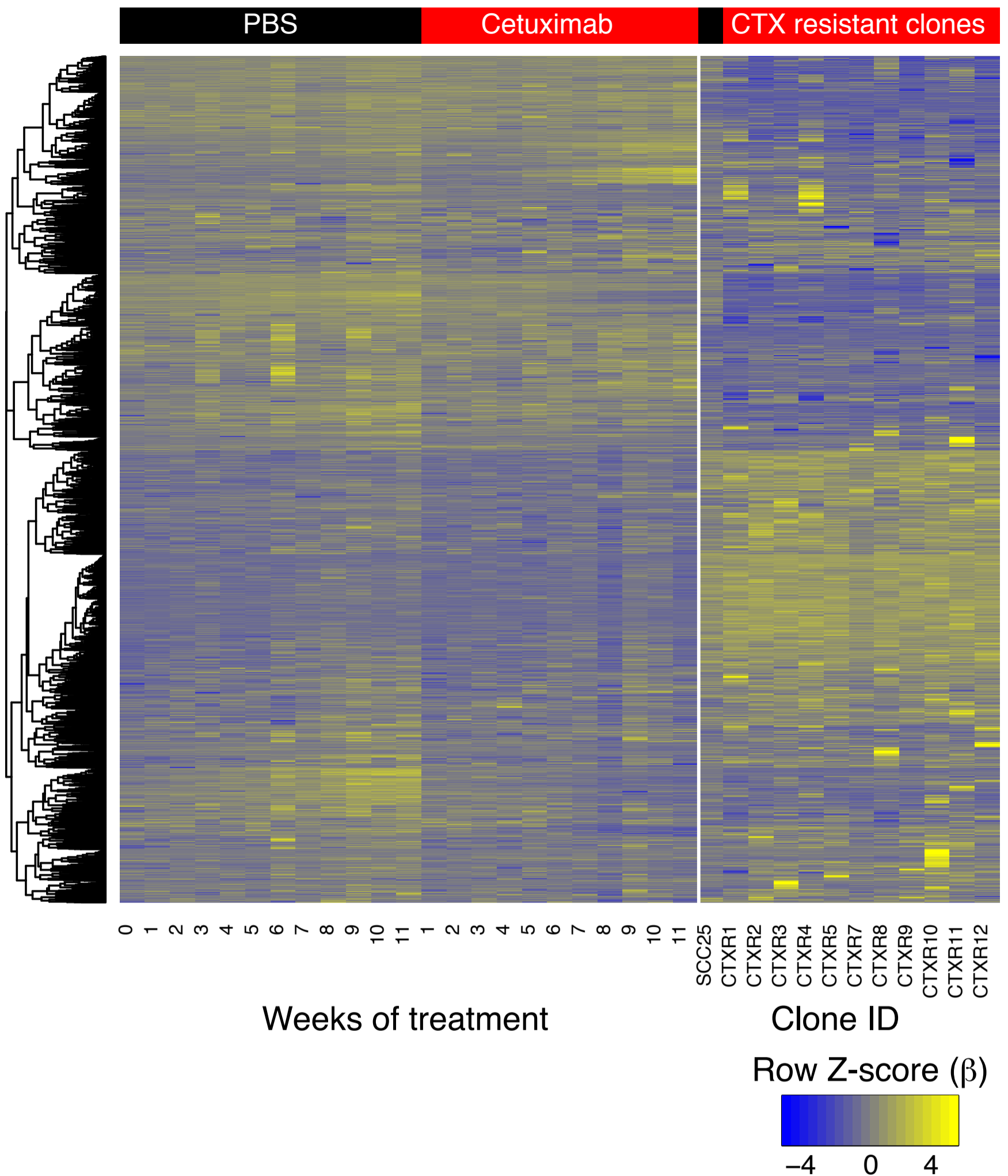
Correlation in CoGAPS gene amplitudes



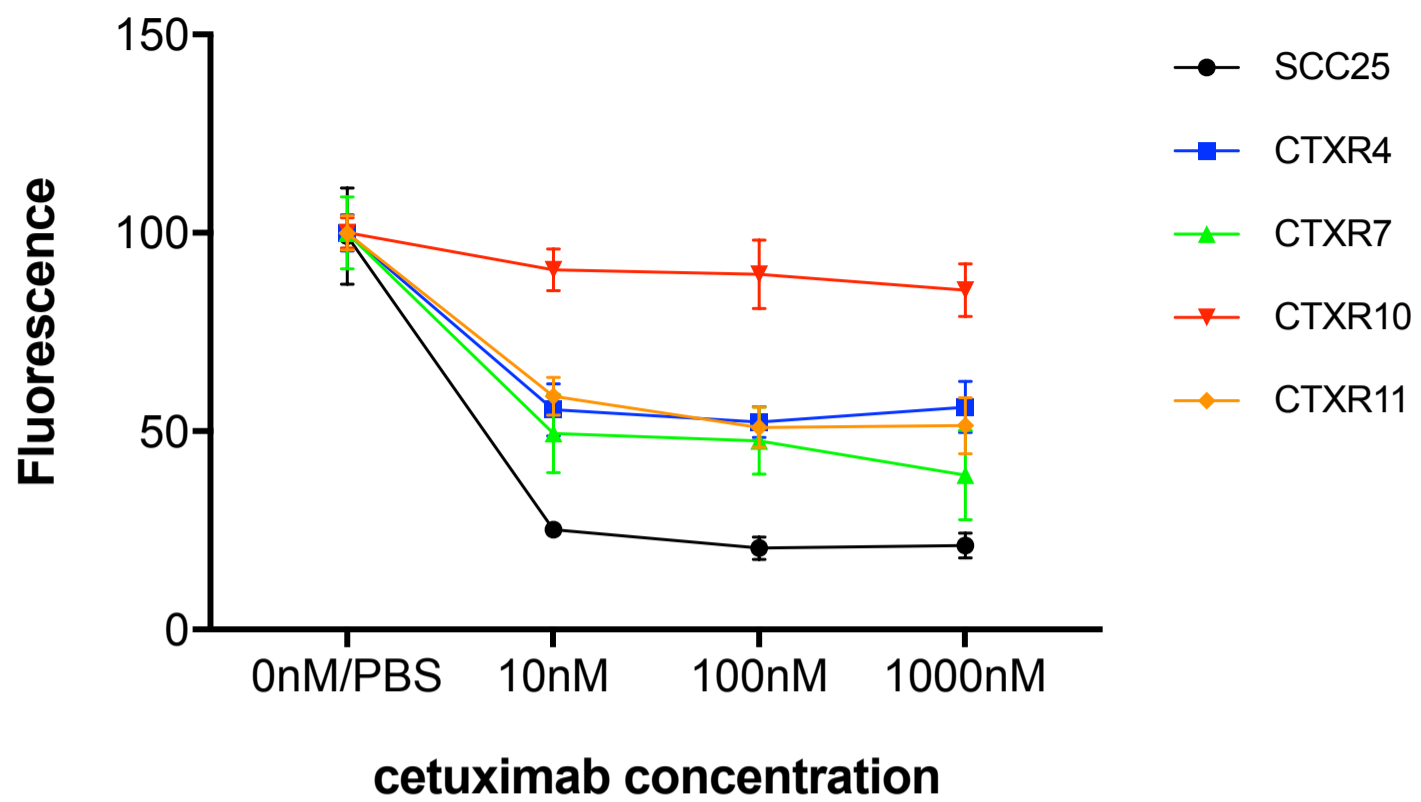
Supplemental Figure 3 - Heatmap of correlation between CoGAPS meta-pathway values corresponding to patterns in DNA methylation (columns) and gene expression (rows). Patterns are colored according to matching defined in Figure 4.



Supplemental Figure 4 – Heatmap of gene expression values for 11 generations of SCC25 cells treated with PBS as control (black columns labeled PBS) and with 100nM of cetuximab (red columns labeled cetuximab) to acquire resistance and gene expression data from independent, stable cetuximab resistant clones in absence of cetuximab treatment (CTX resistant clones).

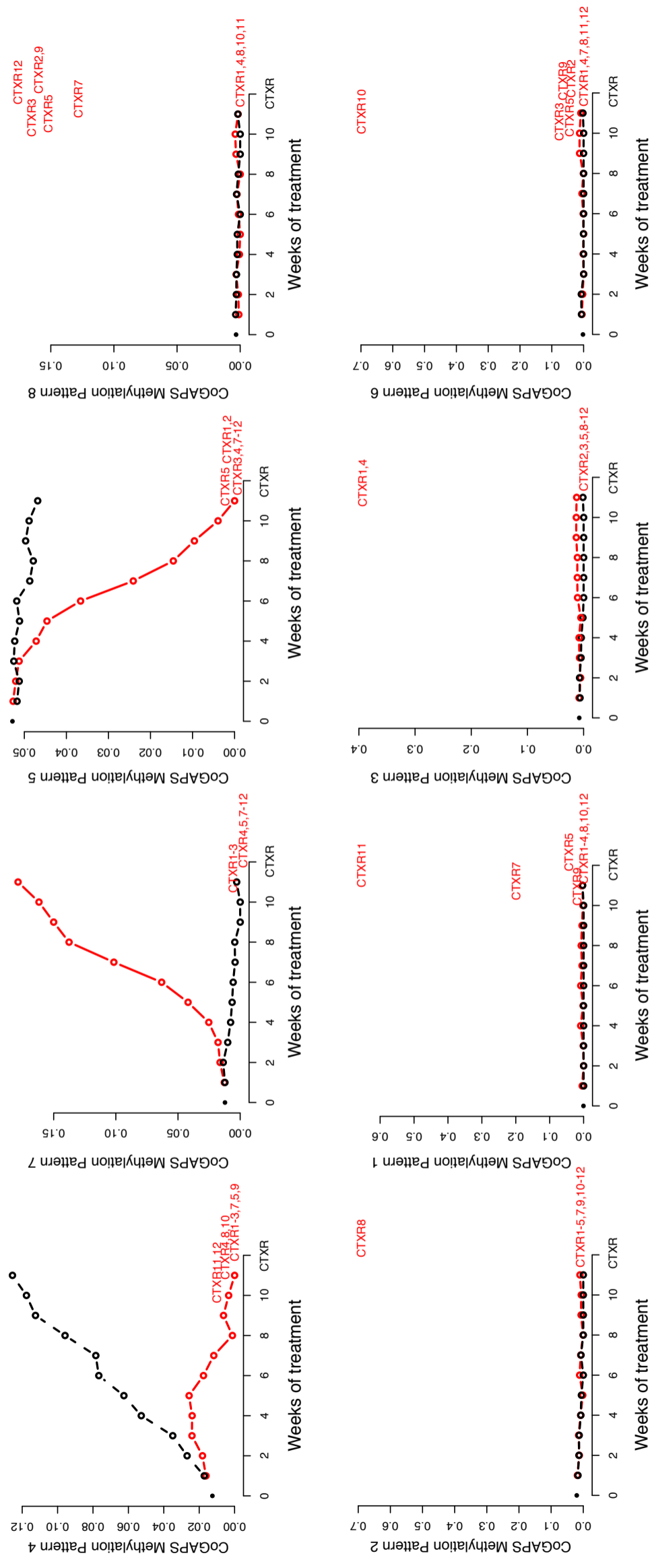


Supplemental Figure 5 - Heatmap of DNA methylation values for 11 generations of SCC25 cells treated with PBS as control (black columns labeled PBS) and with 100nM of cetuximab (red columns labeled cetuximab) to acquire resistance and gene expression data from independent, stable cetuximab resistant clones in absence of cetuximab treatment (CTX resistant clones).

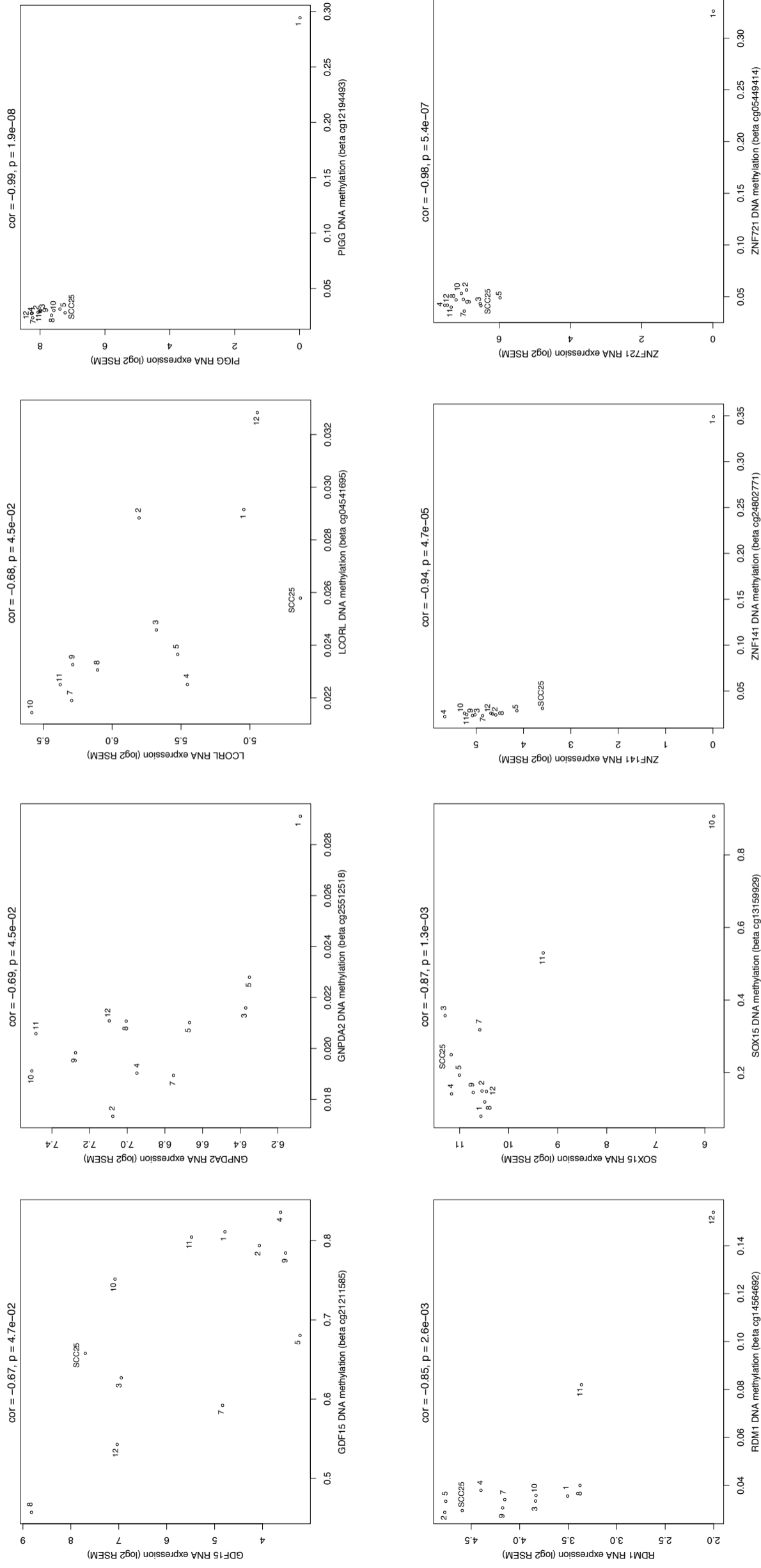


Supplemental Figure 6 – Cell proliferation assay using AlamarBlue (Invitrogen, Carlsbad, CA) to compare proliferation rates under different concentrations of cetuximab in the resistant single cell clones (CTXR4, 7, 10 and 11) and the parental SCC25 cell line to confirm resistance to cetuximab when treated with different concentration of the drug.

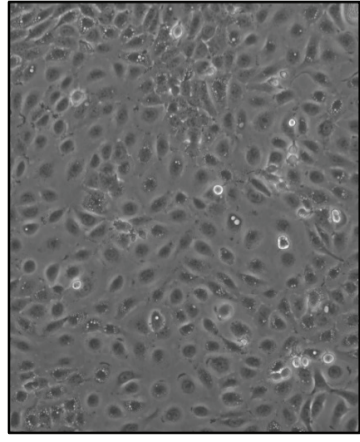
(a) -○- Cetuximab resistant generations (C1 - C11)
-○- PBS control generations



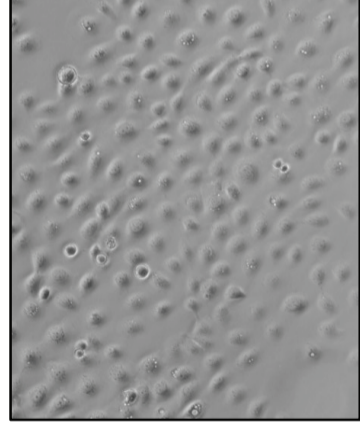
Supplemental Figure 7 - CoGAPS patterns from DNA methylation of combined time course and stable cetuximab resistant clones. Patterns are sorted by associated with time course or single cell clones. Patterns specific to individual clones are sorted according to their trend within the relationship of *FGFR1* expression and correlation in **Figure 4c**.



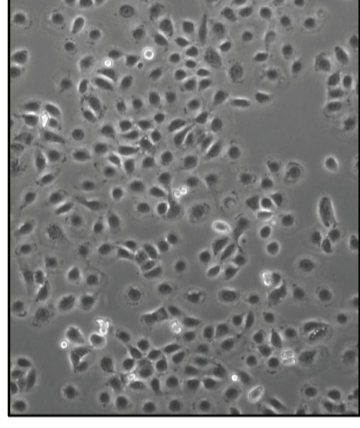
Supplemental Figure 8 – Epigenetically regulated pattern marker genes associated with resistance presenting anti-correlation between gene expression and DNA methylation in the cetuximab single cell resistant clones.



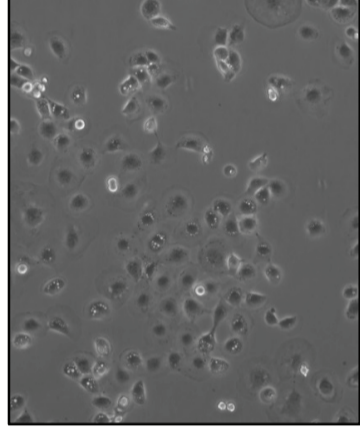
SCC25



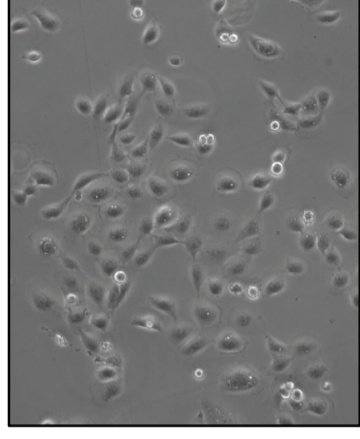
CTXR1



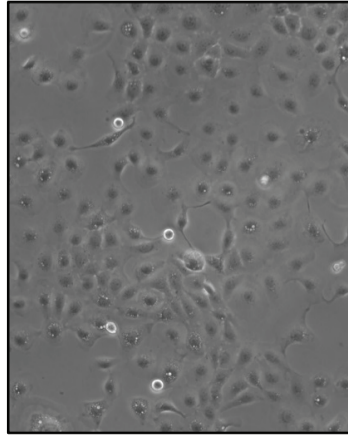
CTXR2



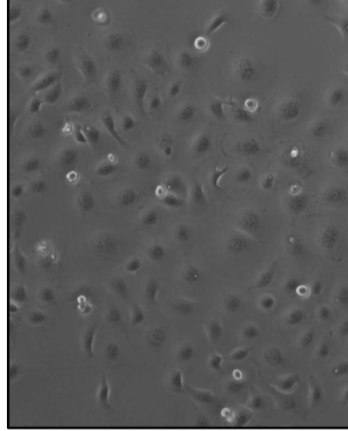
CTXR3



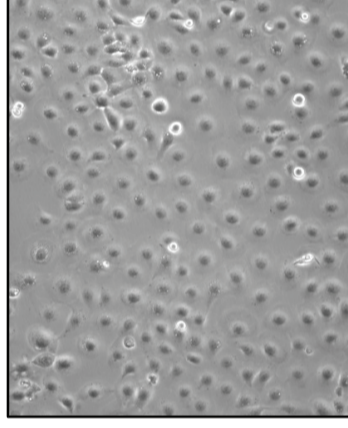
CTXR4



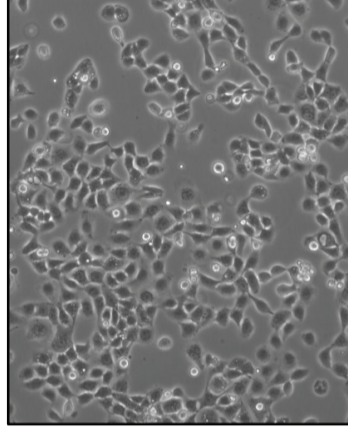
CTXR5



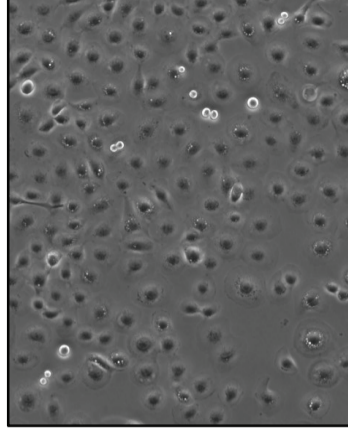
CTXR6



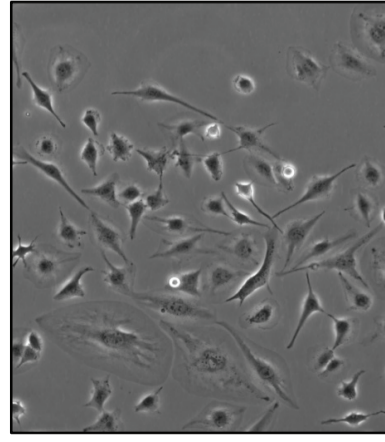
CTXR7



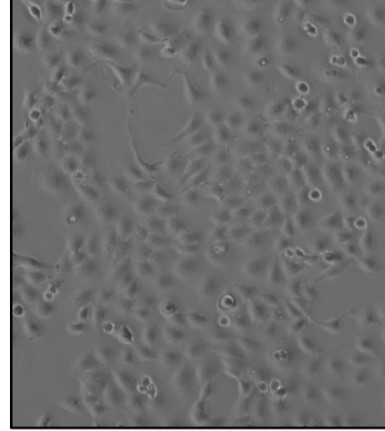
CTXR8



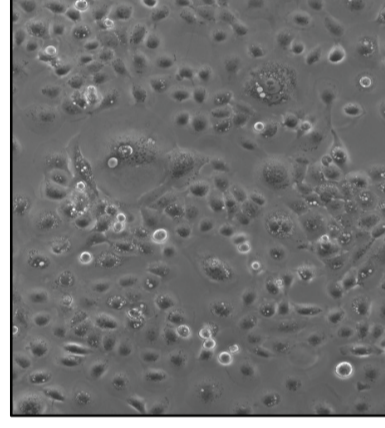
CTXR9



CTXR10



CTXR11



CTXR12

Supplemental Figure 9 - Brightfield microscopy images of the representative clones' morphology above with corresponding clone specific CoGAPS patterns of DNA methylation above.