Use Case 15 [optional]: Exploration of Estrogen Receptor alpha (ERa) Network in Breast Cancer Cells

Epigenome Informatics Workshop

Bioinformatics Research Laboratory

SPARK and GREAT tools References

Nielsen, C., Younesy, H., O'Geen, H., Xu, X., Jackson, A., Milosavljevic, A., Wang, T., Costello, J., Hirst, M., Farnham, P., et al. (2012). Spark: a navigational paradigm for genomic data exploration. Genome Research *22*, 2262–2269.

McLean, C., Bristor, D., Hiller, M., Clarke, S., Schaar, B., Lowe, C., Wenger, A., and Bejerano, G. (2010). GREAT improves functional interpretation of cis-regulatory regions. Nature Biotechnology *28*, 495–501.

The data for this use case was obtained from the following references

Kittler, R., Zhou, J., Hua, S., Ma, L., Liu, Y., Pendleton, E., Cheng, C., Gerstein, M., and White, K. (2013). A Comprehensive Nuclear Receptor Network for Breast Cancer Cells. Cell Reports.

Hua, S., Kittler, R., and White, K. (2009). Genomic antagonism between retinoic acid and estrogen signaling in breast cancer. Cell *137*, 1259–1271.

Use Case 15 [optional]: Exploration of Estrogen Receptor alpha (ERa) Network in Breast Cancer Cells

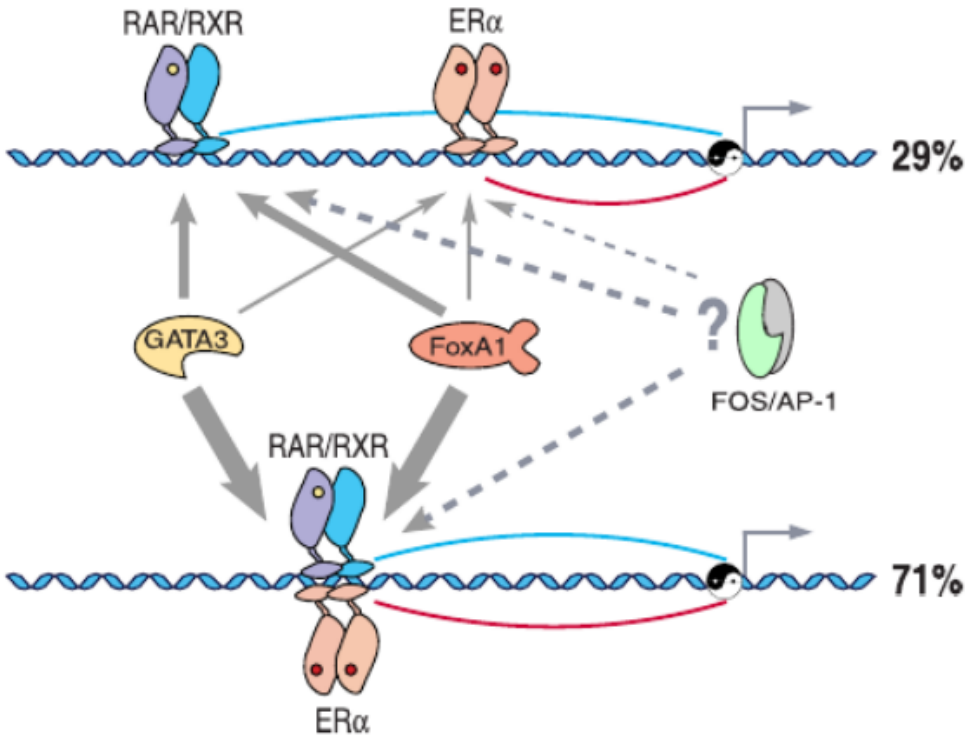
Background:

In breast cancer, estrogen receptor alpha (ERa) is known to play a major role in carcinogenesis and cancer progression. It drives proliferation in about 60-70% of breast cancer patients. Therefore, ERa is one of the main targets in breast cancer therapy. However, recently presence and importance of other nuclear receptors in breast cancer had been shown. Proper understanding of several additional nuclear receptors role in breast cancer may provide better diagnostic markers or novel targets for therapy.

Previous work mapping ERa binding sites genome-wide revealed that FoxA1 is required for ERa binding. However, mapping of retinoic acid receptor (RAR) nuclear receptors showed widespread antagonistic interaction of liganded RARs with ERa in the regulation of breast cancer-associated genes.

Cell 137, 1259-1271 (2009)

Model for the Antagonistic Regulation of Target Genes by RAR and ERa



FoxA1 has been implicated in recruitment of ERa to distal sites. Hua et al showed that FoxA1 similarly required for RAR recruitment to genomic binding sites. Many of the genomic regions bound by RAR overlap with ERa. Majority of the overlap regions (71%) have shared binding regions of ERa and RARs. Transcriptional analysis indicate that RARs and ERa tend to exhibit antagonistic effects on the transcription of target genes. Based on the known functions of their target genes in breast cancer, ERa and RARs appear to be 'yin and yang' for the genetic regulation of proliferation and survival that are promoted by ERa and inhibited by RARs.

Cell 137, 1259-1271 (2009)

Comprehensive Nuclear Receptors profiling in Breast Cancer Cells

Kittler et al, Cell 2013 - Performed ChIP-chip profiling of various factors in MCF-7 cells (Breast Cancer Cells)

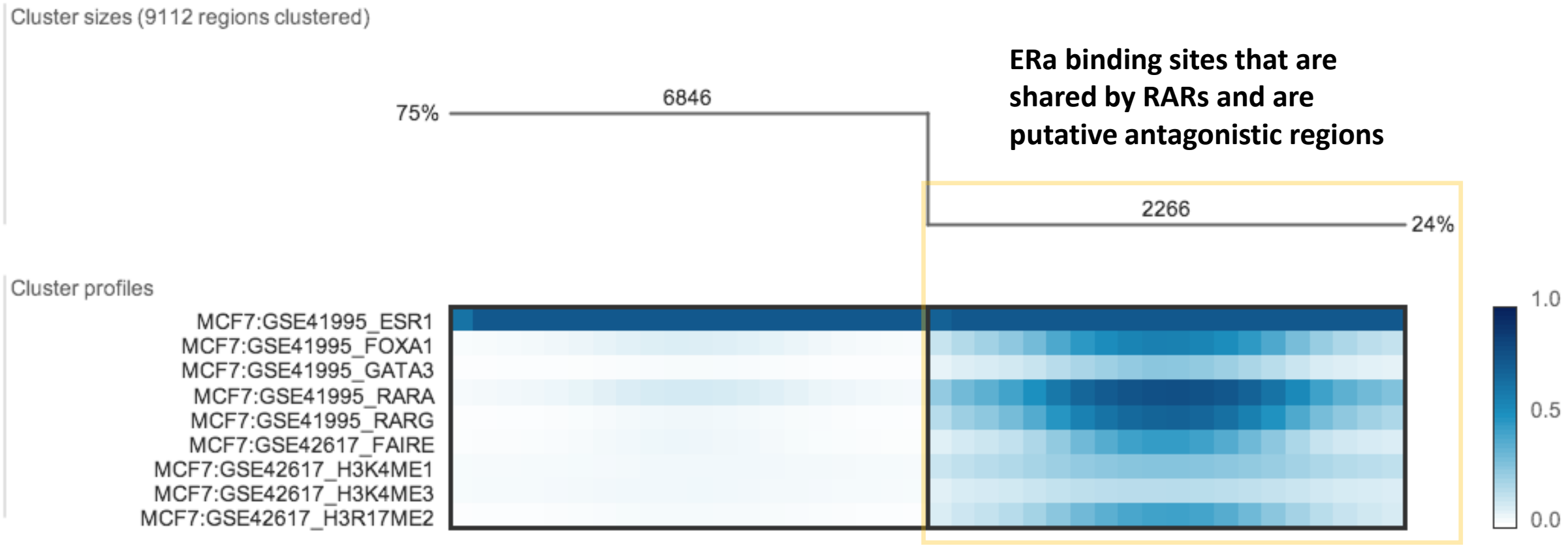
- 24 Nuclear receptors
- 6 chromatin states
- 14 breast-cancer-associated transcription factors

This dataset is already uploaded in Genboree for you.

Using SPARK tool in Genboree, we would like to demonstrate, how such dataset can be used to determine genes that are regulated by ERa and RARs antagonistic interaction.

SPARK analysis determines antagonistic regions shared by ERa and RARs

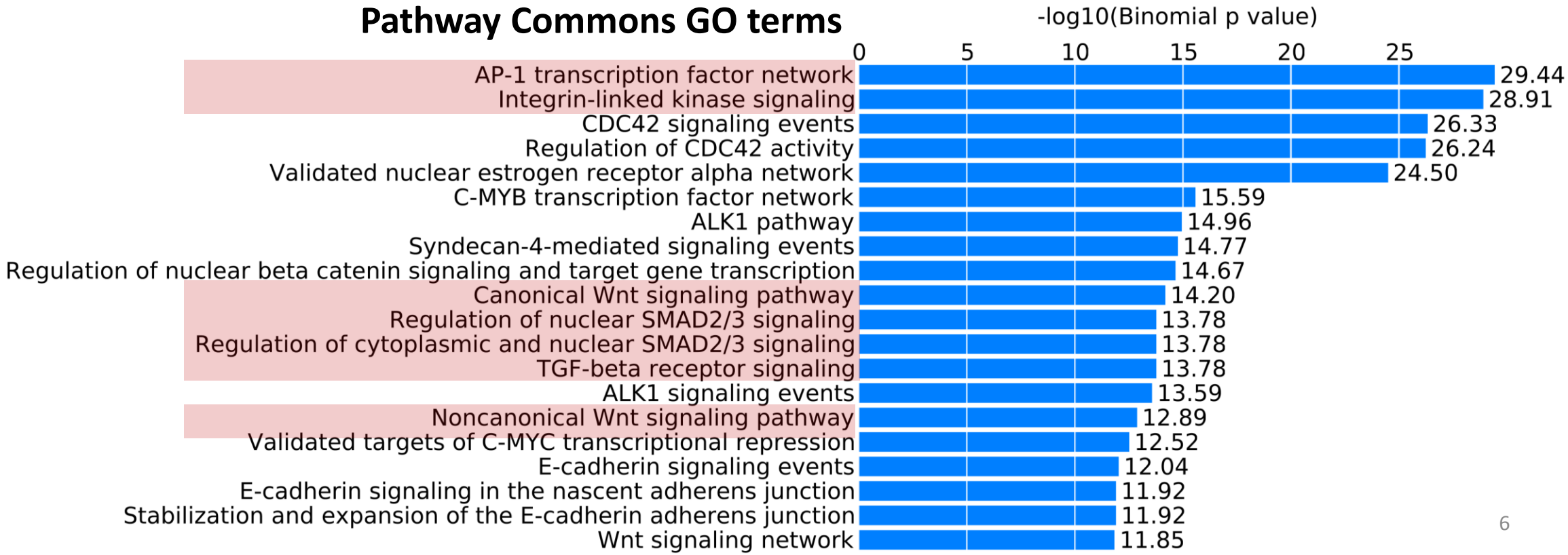
ERa binding sites



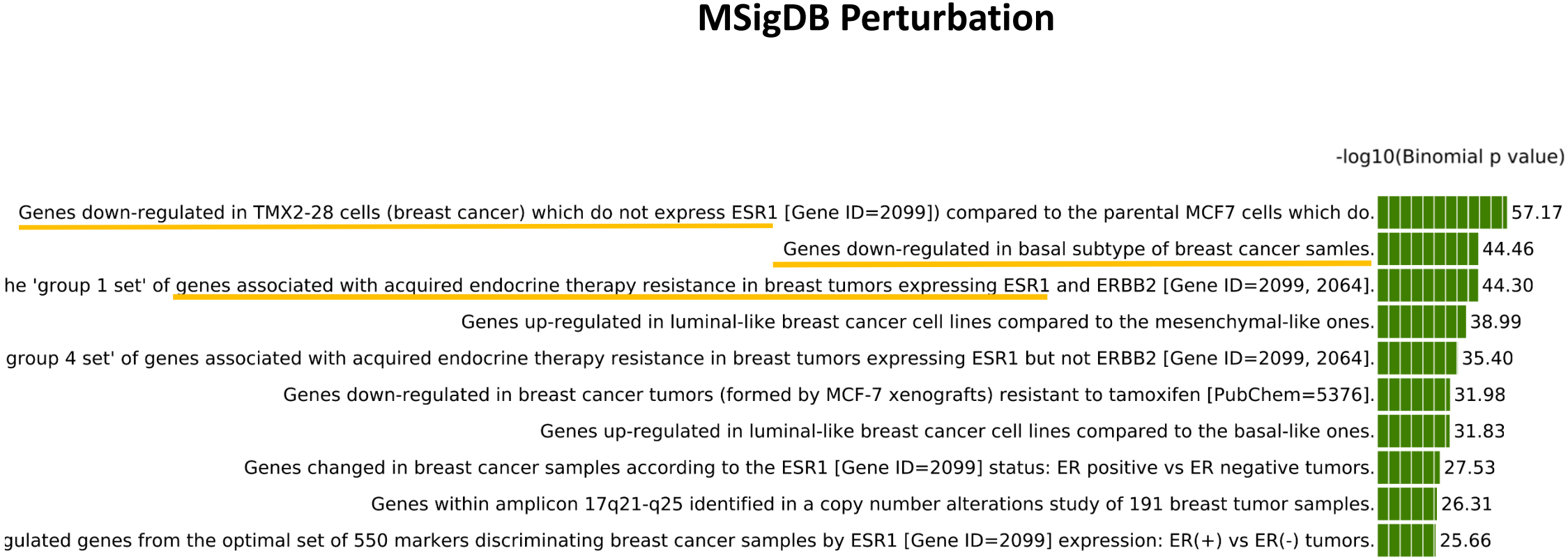
ERa binding sites that are shared by RARs and are putative antagonistic regions

Genes regulated by antagonistic interaction between ERa and RARs are involved in pathways associated with Breast Cancer progression

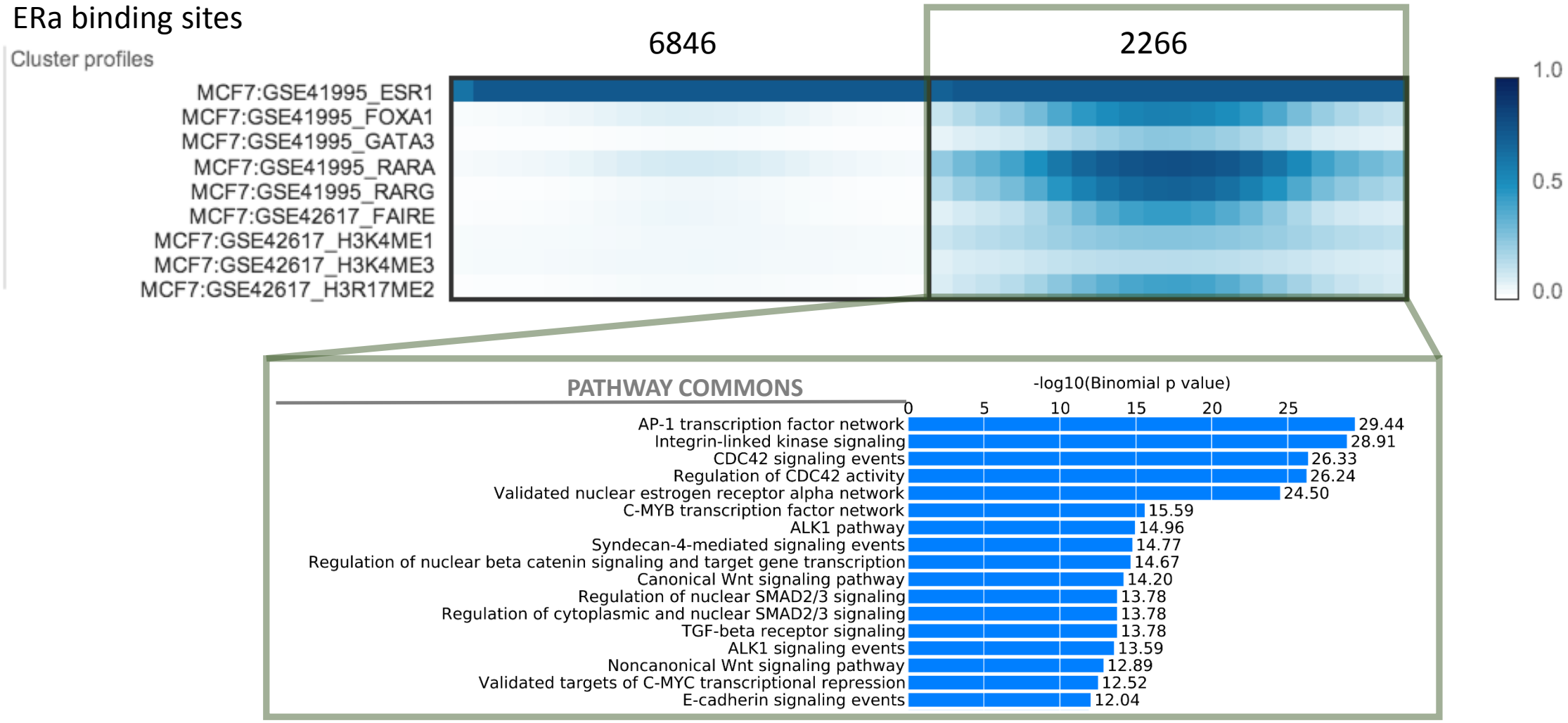
GREAT analysis is used to associate cis-regulatory elements to gene sets
Following are Pathway Commons GO terms enriched by these gene sets



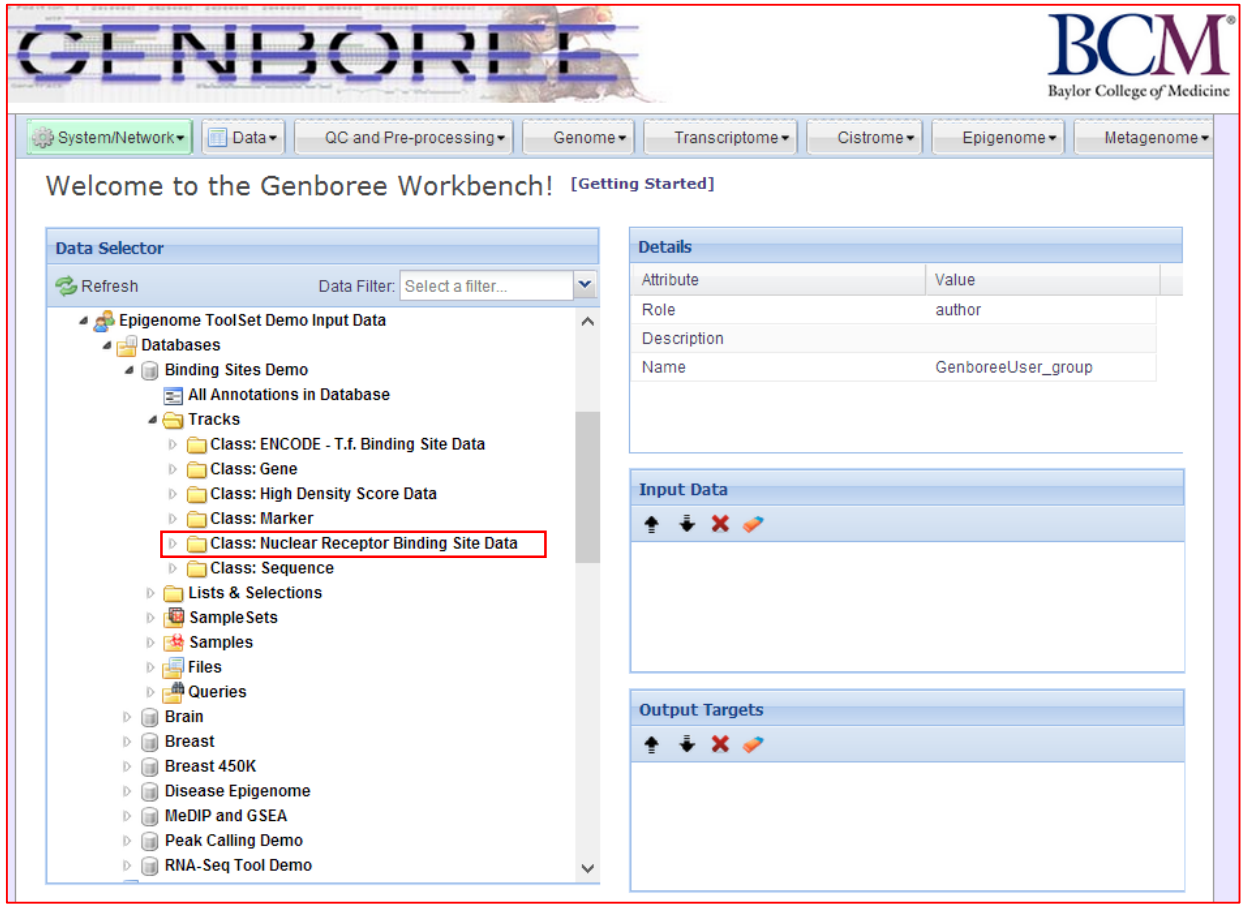
Genes associated by antagonistic interaction are regulated by ERa and required for breast cancer progression

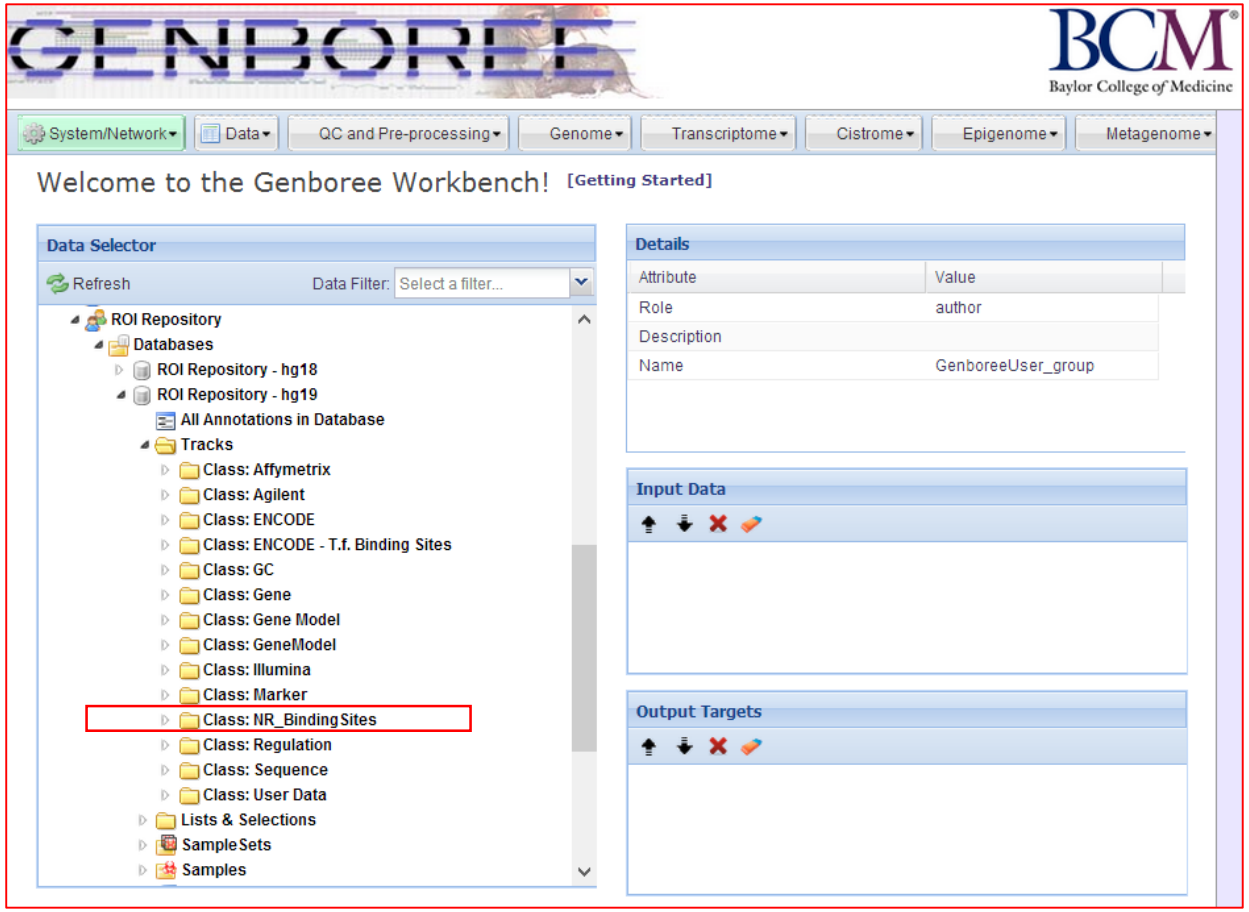


Antagonistic regions between ERa and RARs do regulate genes and pathways that are involved in breast cancer progression



Use case instructions for this is similar to use case example of RAD21 in ESCs. Datasets required for the analysis are located as follows-





Nuclear Receptor binding site score data are located in **Epigenome ToolSet Demo Input Data > Databases > Binding Sites Demo > Tracks > Class: Nuclear Receptor Binding Site Data**

Nuclear Receptor binding site/region of interests (ROIs) are located in **ROI Repository > Databases > ROI Repository – hg19 > Tracks > Class:NR_BindingSites**