



The Epigenetic Component of TCGA – Discovery of DNA Hypermethylated Genes in Glioblastoma

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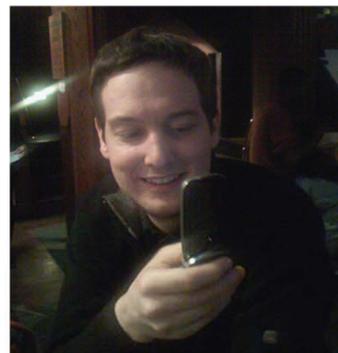
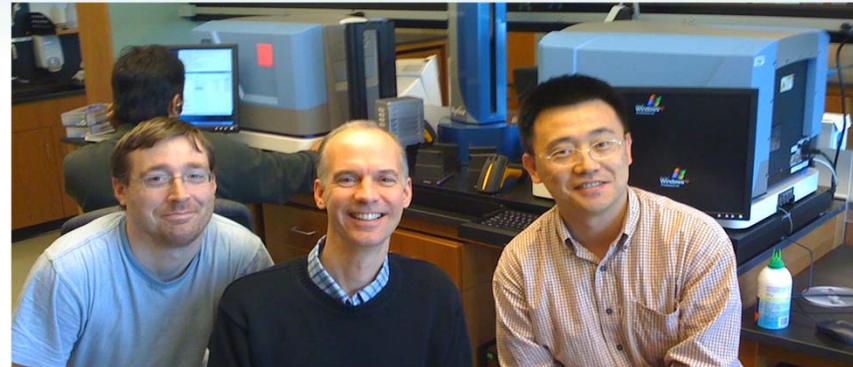
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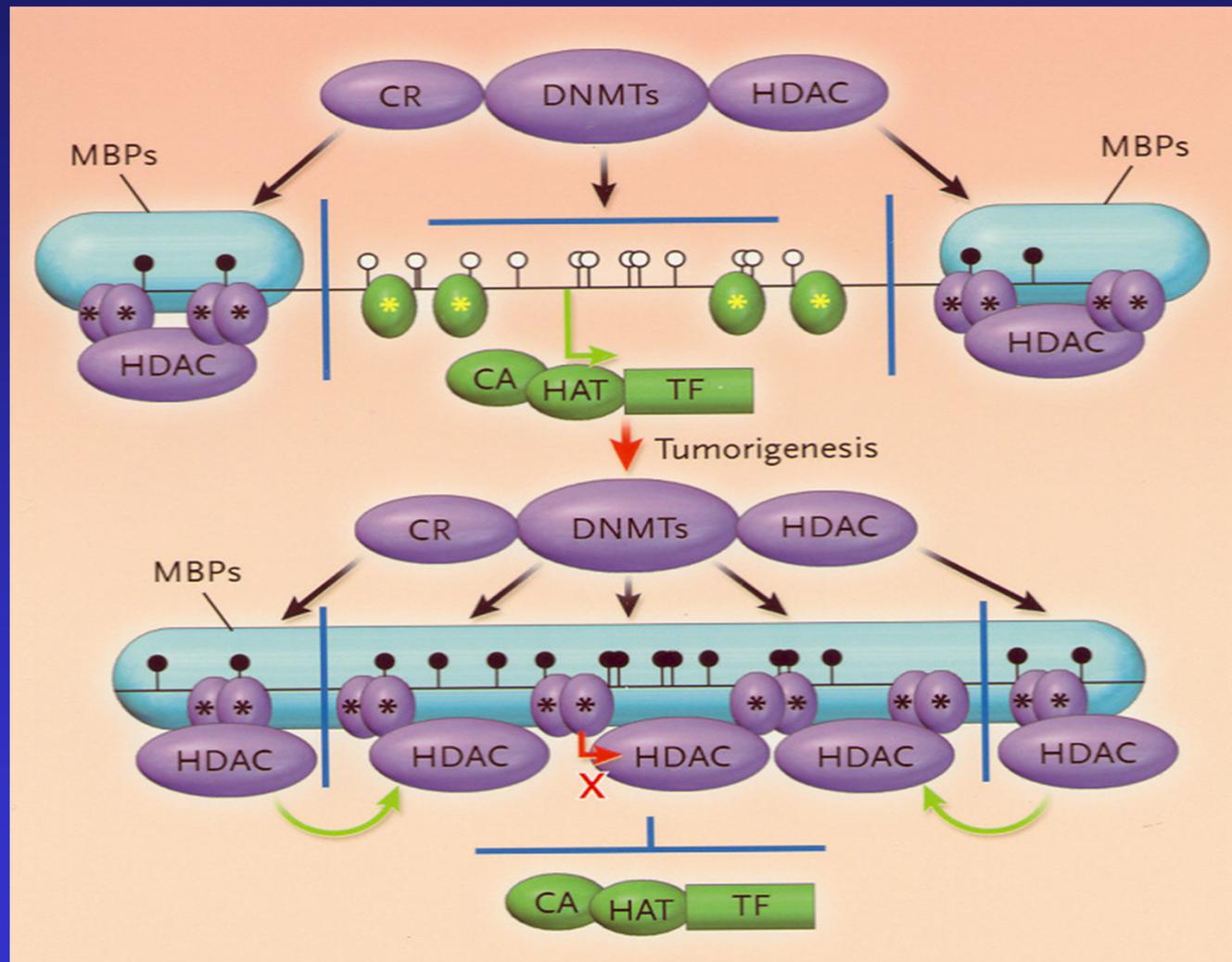


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DNA hypermethylation, and associated transcriptional repression, is, perhaps, the leading mechanism for loss of gene function in cancer.

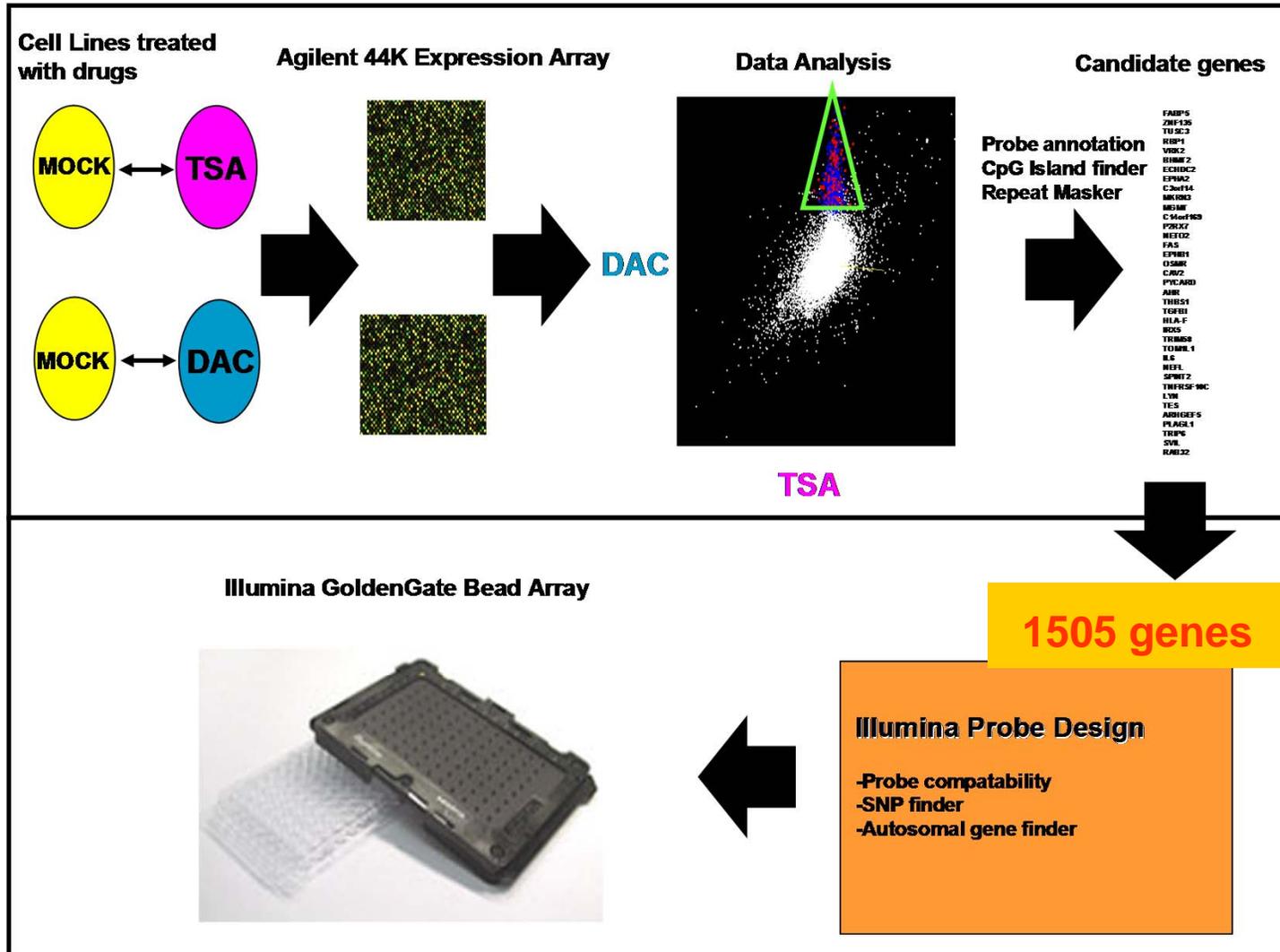


Genes include many which are silenced in pre-invasive stages and encode for stem cell, developmental pathway, etc proteins

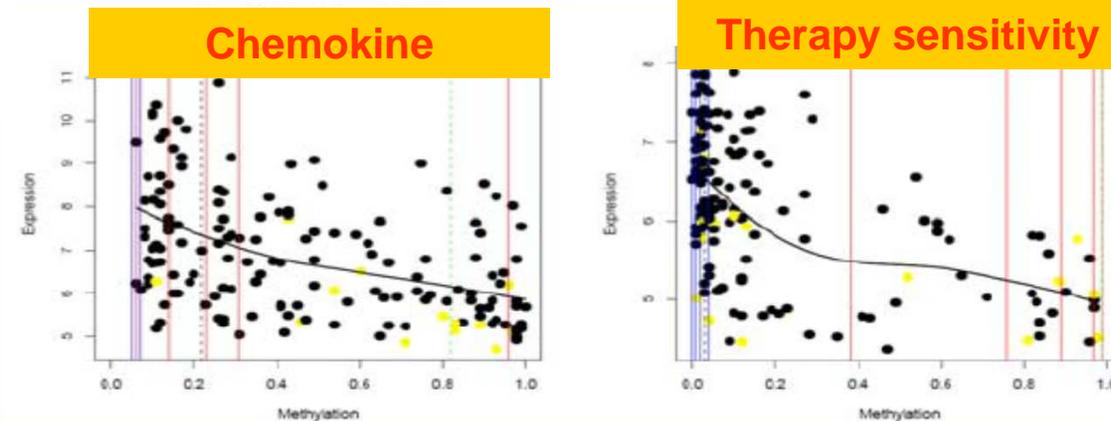
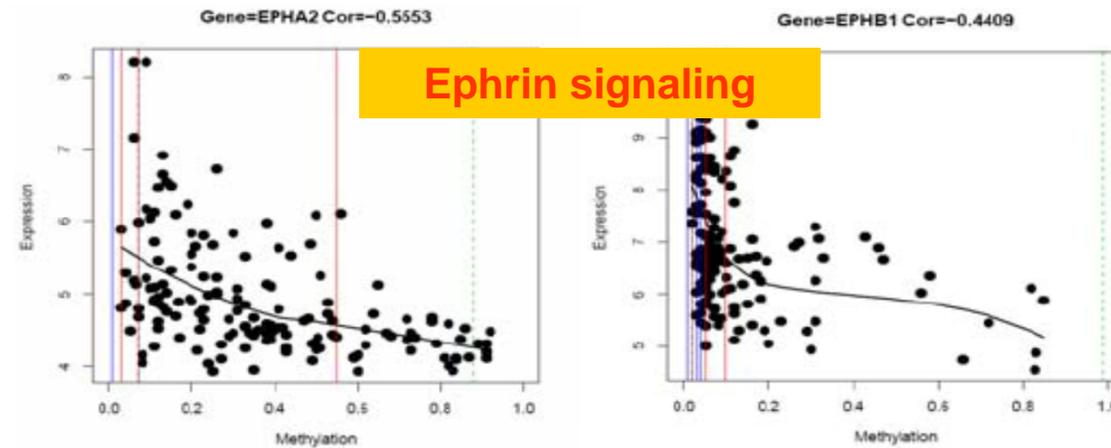
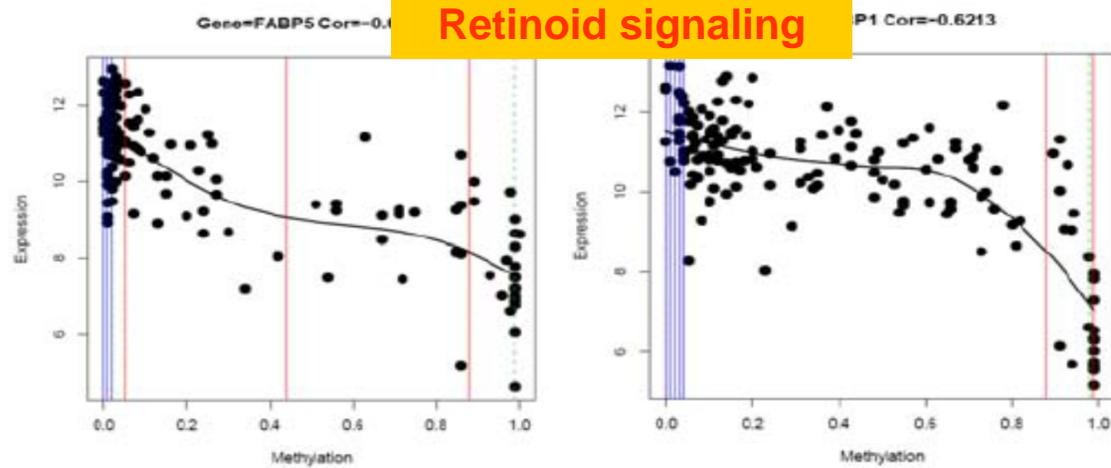
Herman and Baylin, NEJM, 2003

Approach to DNA Hypermethylated Gene Discovery in TCGA

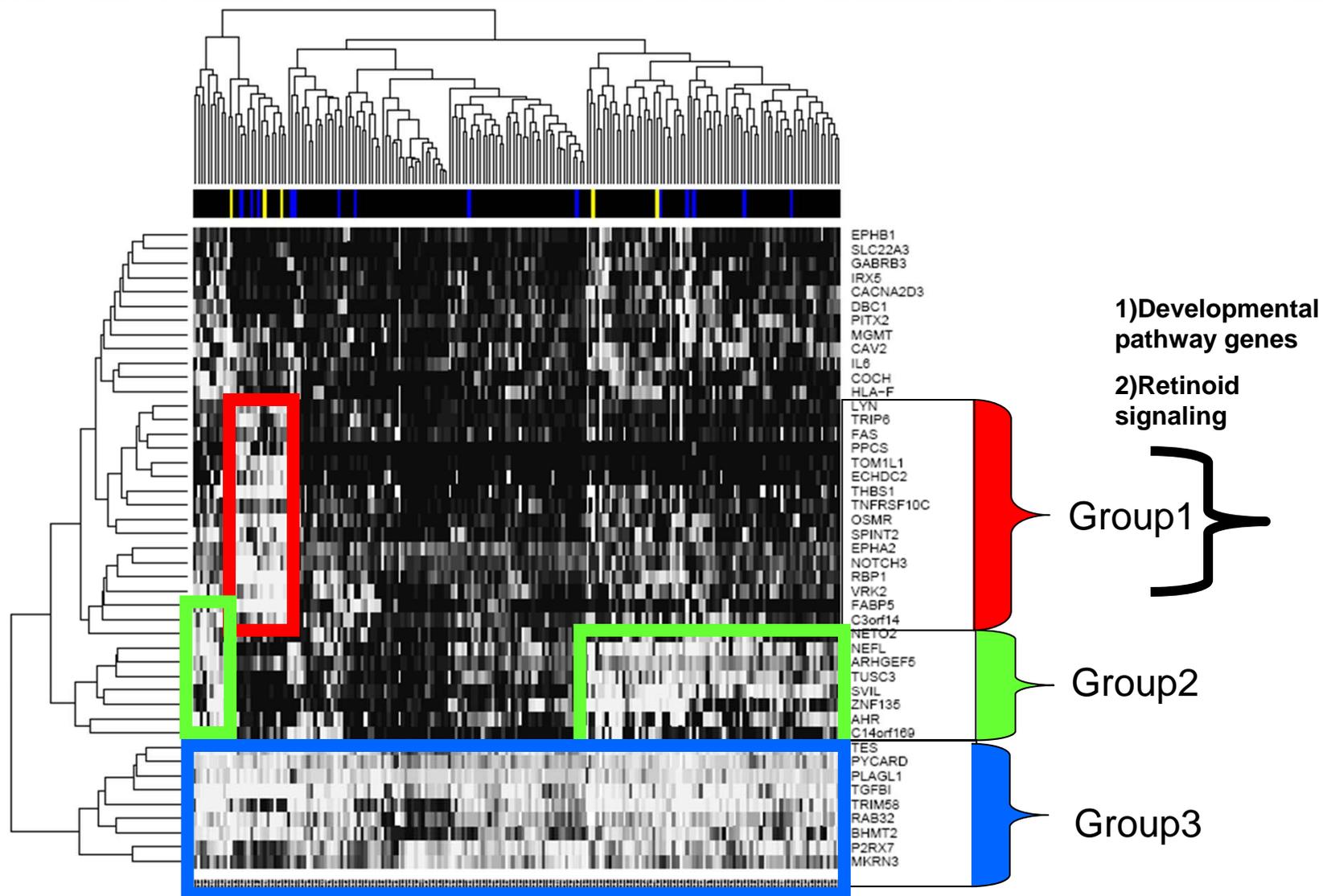
Supplementary Figure 1.



The association of DNA Methylation With Gene Expression and copy number shows integrative power of TCGA

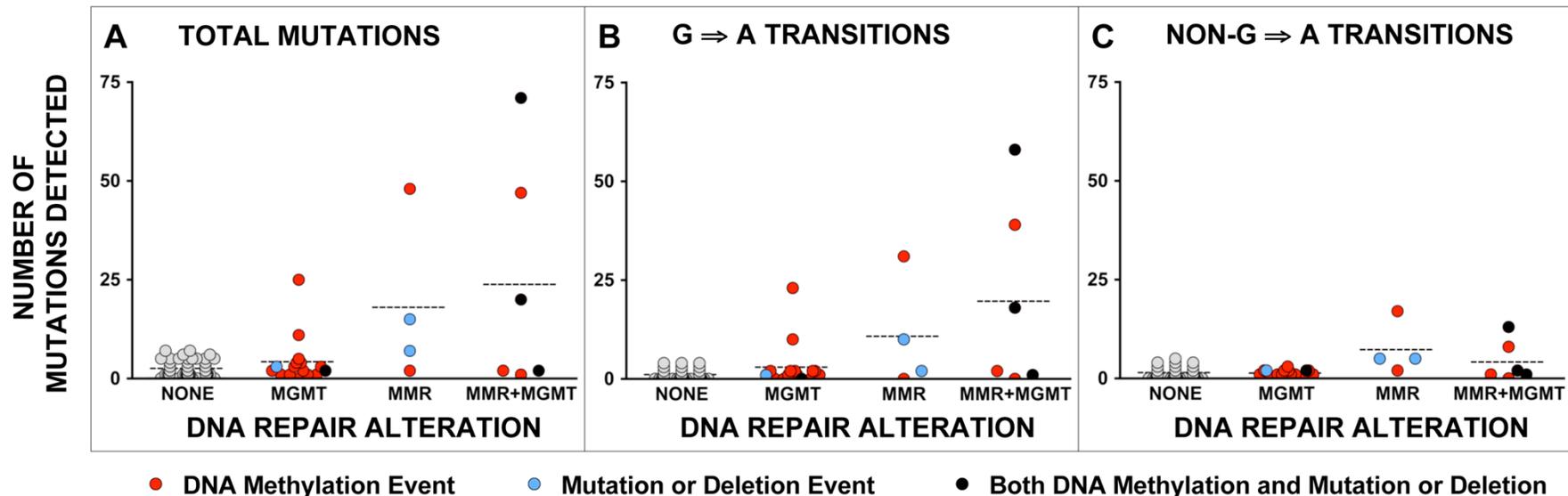


Heat map for the top 45 DNA hypermethylated genes defines groups of GBM with important features





DNA hypermethylation of DNA Repair Genes accounts for the majority of mutations in ~30% of GBM's sequenced – again, the integrative power



Summary

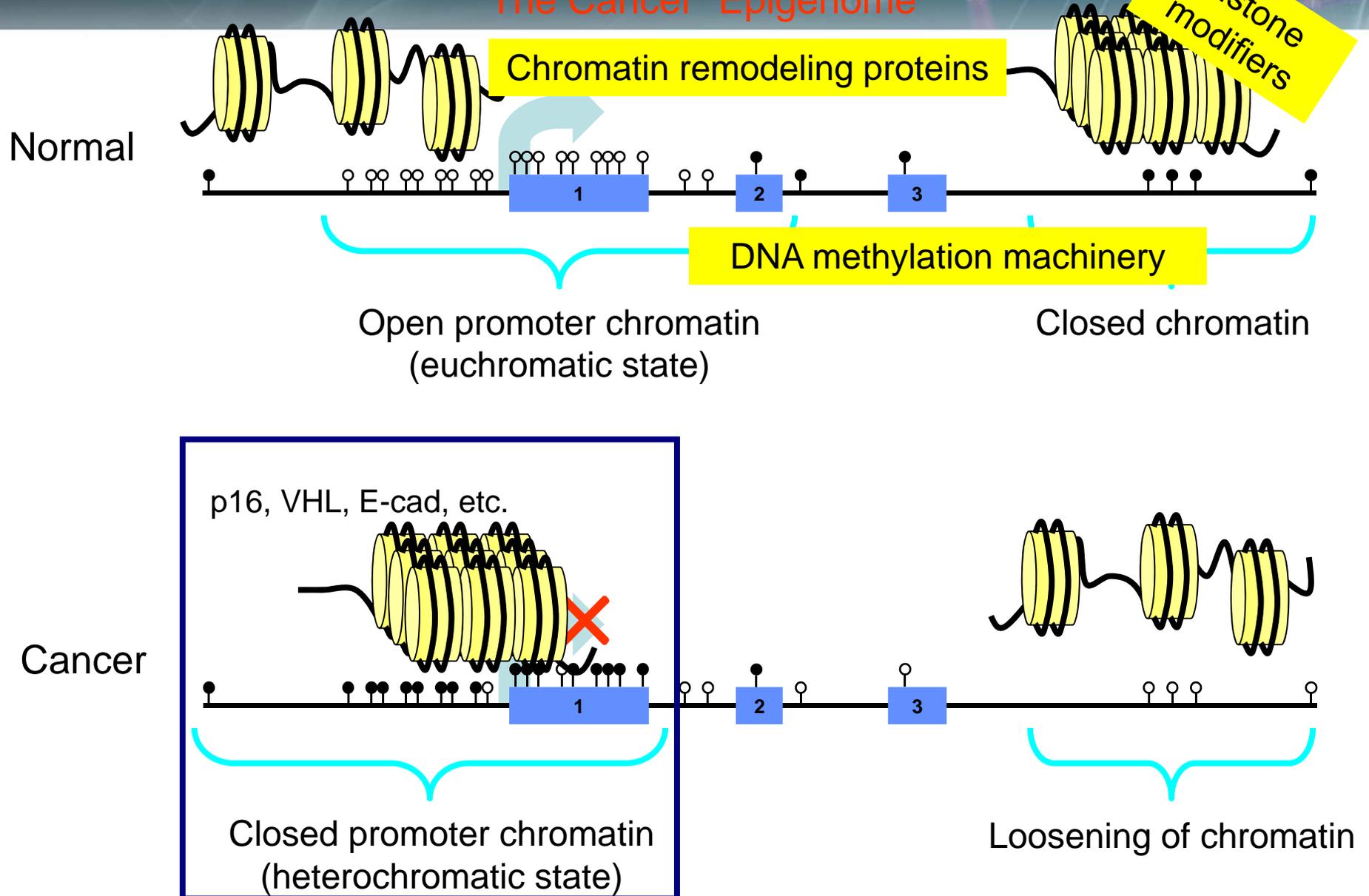


- **Off to a very successful start**
- **Potentially, at least ~300 cancer specific DNA hypermethylated GBM genes identified for ~ 200 primary samples analyzed**
- **Successful integration of hypermethylated genes with expression, ROI, and mutation data**
- **DNA hypermethylated genes are pointing towards sub-groups of GBM which may have important biological and clinical implications**
- **Large scale demonstration of how epigenetic changes can determine a large percentage of gene mutations in cancer**

Altered Chromatin Status in Cancer

The Cancer "Epigenome"

THE CANCER GENOME ATLAS



The Future



- **Continue, and expand to full coverage, the search for cancer specific , promoter CpG island DNA hypermethylation –and include miRNA's & other non-coding RNA's**
- **The above may be facilitated by an Illumina platform capable of querying ~20,000 promoters; being tested in TCGA at present**
- **Consider assays of global histone modifications and DNA methylation levels – these may correlate in important ways to key maturation stages of cancers investigated**
- **Look carefully at emerging status of platforms that would allow all patterns of DNA methylation and chromatin to be monitored (ChIP/seq – subsets of tumors?)**