Elucidating gene networks precipitating relapse in CAR T-Cell treated diffuse large B-cell lymphoma

A case for multiple CCA and heirarchical tree trimming

Will Patterson Bo Hu (Advisor)

8/28/2020

Outline

Hypothesis: Integration of multi-omics signals will elucidate gene networks involved in DLBCL relapse after CAR T-cell therapy.

1. **What**: Diffuse Large B-Cell Lymphoma
2. **Why**: Approximately half of patients with DLBCL treated with CAR T-cells will relapse
3. **How**: Multi-omics integration using sparse multiple cannonical correlation analysis

What: Diffuse Large B-Cell Lymphoma

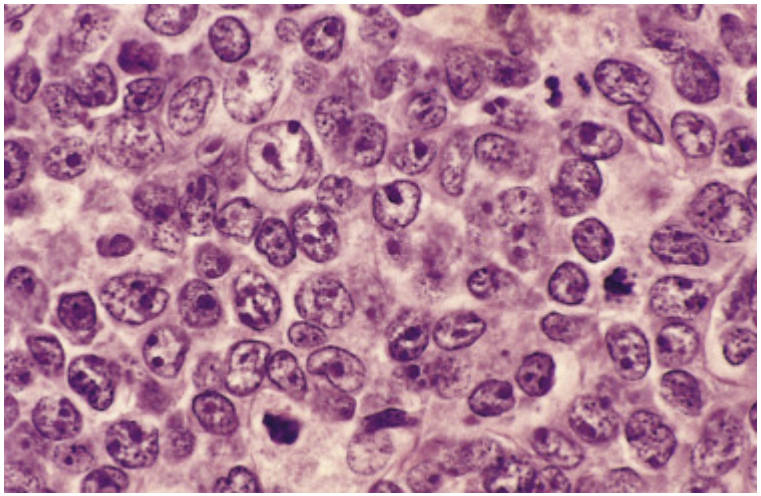


Figure 1: Micrograph of DLBCL (Field stain)

- Most common non-Hodgkin lymphoma (5.6 per 100,000 persons per year), arises from mature B lymphocytes
- Average 5-year relative survival rate of 63% (72% for all NHL)
- **Treatment:** R-CHOP/EPOCH $\rightarrow$ salvage/HCT $\rightarrow$ CAR T-cell

Multiple Canonical Correlation Analysis: Definition

Canonical Correlation Analysis (CCA) finds the relationship between sets of variables by finding their maximally correlated linear combinations.

Given: K sets of observations on same n observations, $\mathbf{X}_1, ..., \mathbf{X}_K$ of dimensions $n \times p_k$, all standardized to mean zero and SD of one

Find: Weights $\mathbf{w}_1, ..., \mathbf{w}_k$, where $\mathbf{w}_k \in \mathbb{R}^{p_k}$, such that the objective function below is maximized

Multiple CCA objective function

$$\text{maximize}_{\mathbf{w}_1,...,\mathbf{w}_K} \sum_{i<j} \mathbf{w}_i^T \mathbf{X}_i^T \mathbf{X}_j \mathbf{w}_j \text{ subject to } ||\mathbf{w}_i||^2 \leq 1, P_i(\mathbf{w}_i) \leq c_i, \forall i$$

(where P_i is the L_1 penalty for i^{th} set)

Extension of sparse mCCA to binary outcomes

Witten and Tibshirani (2009) suggest an extension of sparse mCCA that allows for the incorporation of a two-class outcome. Their method simply treats this $\mathbb{R}^{n \times 1}$ matrix as a third data set. Their objective function takes the form:

Sparse mCCA objective function with binary variables

$$\text{maximize}_{\mathbf{w}_1, \mathbf{w}_2, \mathbf{w}_3} \mathbf{w}_1^T \mathbf{X}_1^T \mathbf{X}_2 \mathbf{w}_2 + \mathbf{w}_1^T \mathbf{X}_1^T \mathbf{y} \mathbf{w}_3 + \mathbf{w}_2^T \mathbf{X}_2^T \mathbf{y} \mathbf{w}_3$$

$$\text{subject to } ||\mathbf{w}_i||^2 \leq 1, P_i(\mathbf{w}_i) \leq c_i, \forall i$$

Extracting gene networks from multiple CCA

Three step process for gene network extraction:

1. Compute the similarity matrix based on the outer products of absolute canonical correlation weights.
2. Apply hierarchical tree cutting to the similarity matrix and extract modules that contain all -omics data types.
3. Visualize networks.

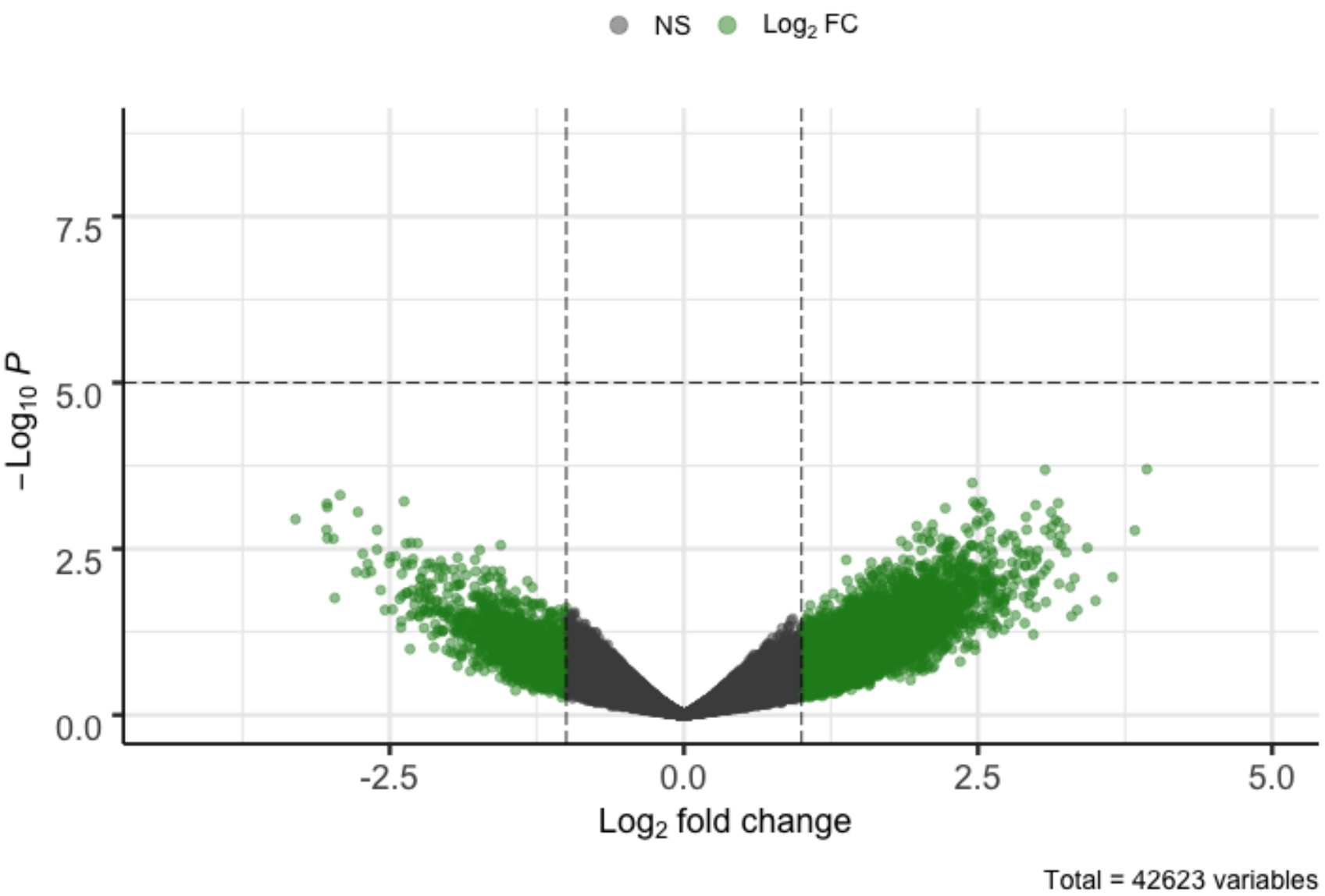
Data

Samples collected from 33 patients with DLBCL

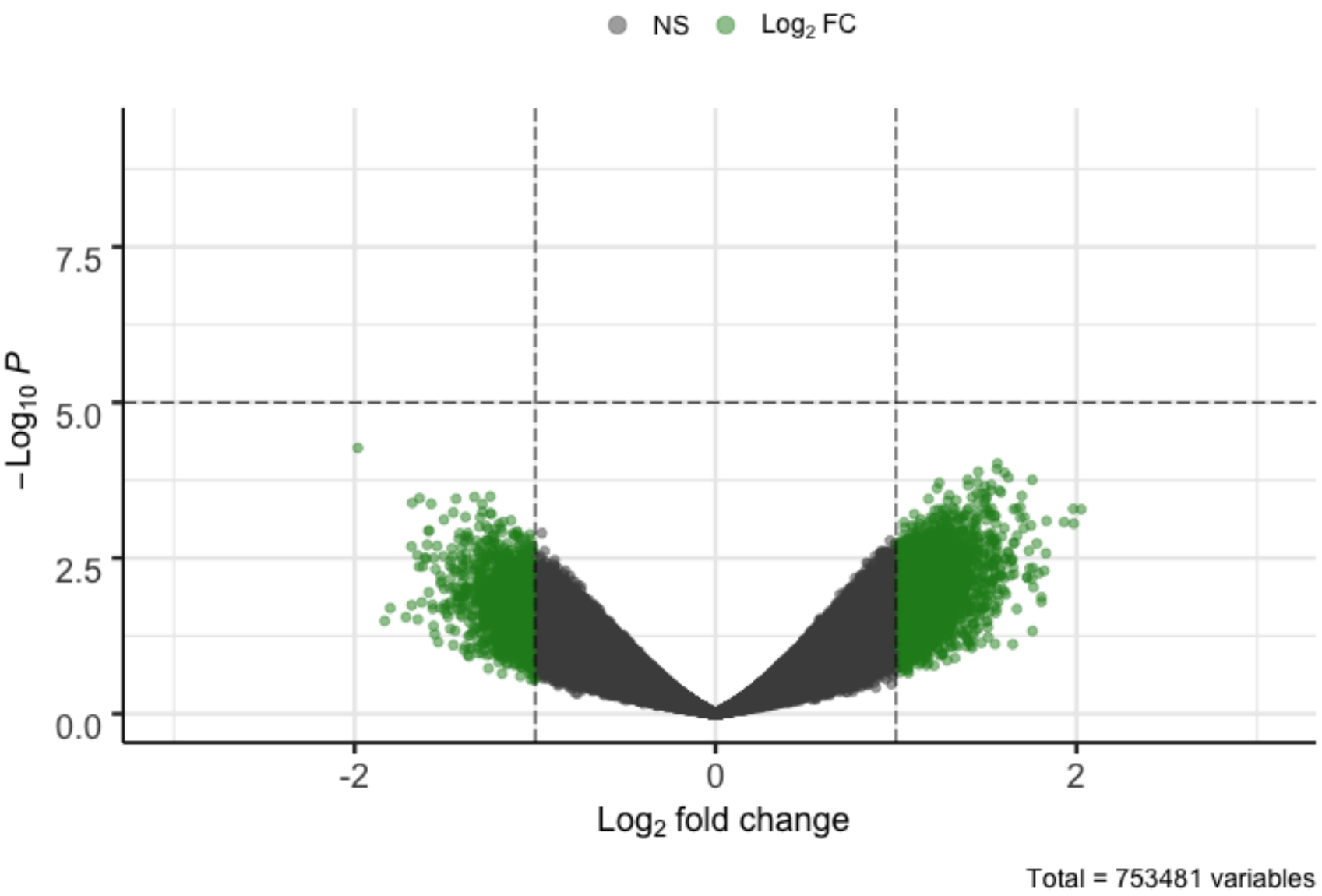
- Diagnostic samples were used to initially diagnose patients with DLBCL
- Relapsed/cured samples were taken post CAR T-cell treatment
- Relapsed/cured samples are not necessarily from same diagnostic individual

Status	n
Cured	9
Diagnostic	13
Relapsed	11

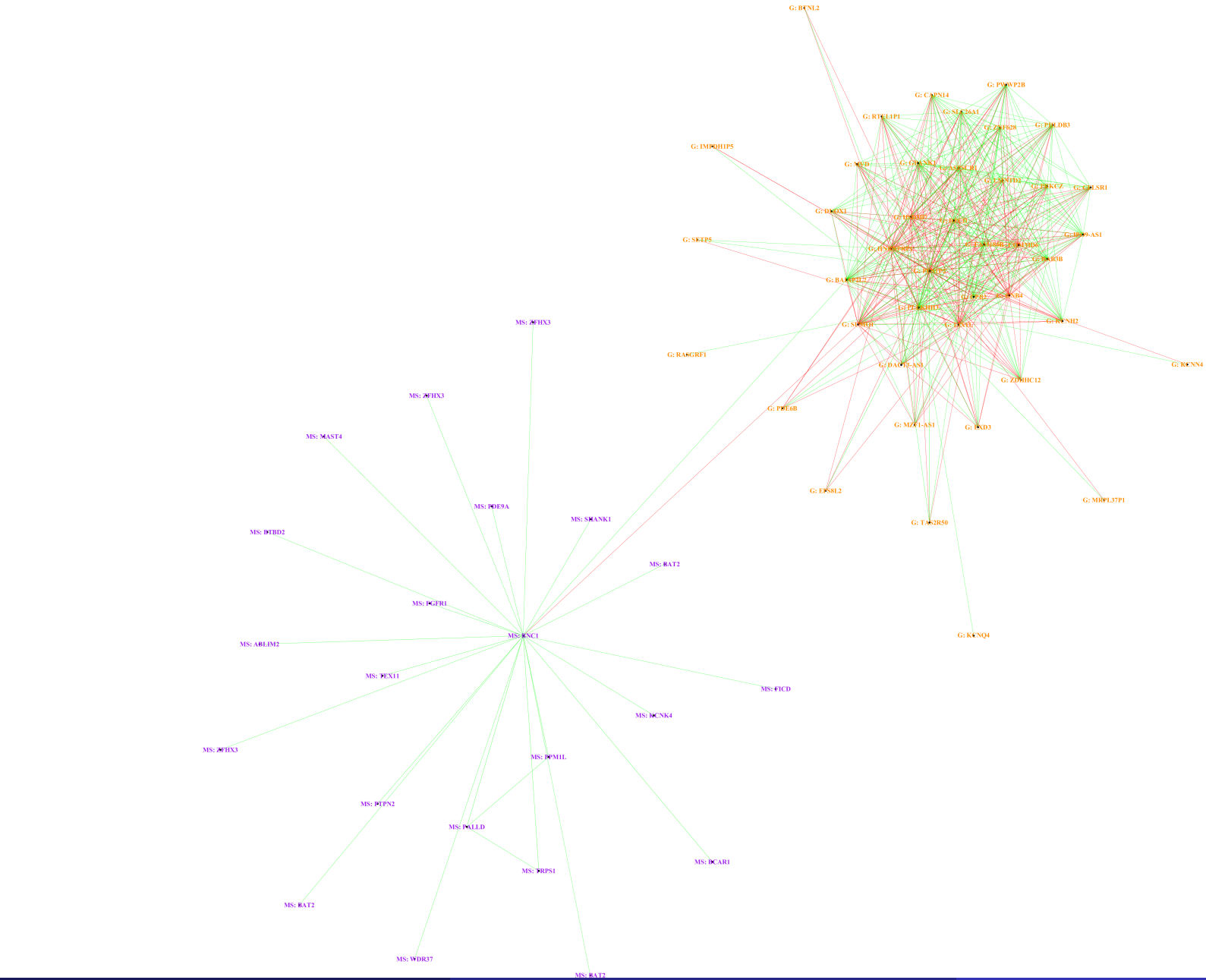
Diagnostic v. Relapsed Samples: Gene Expression



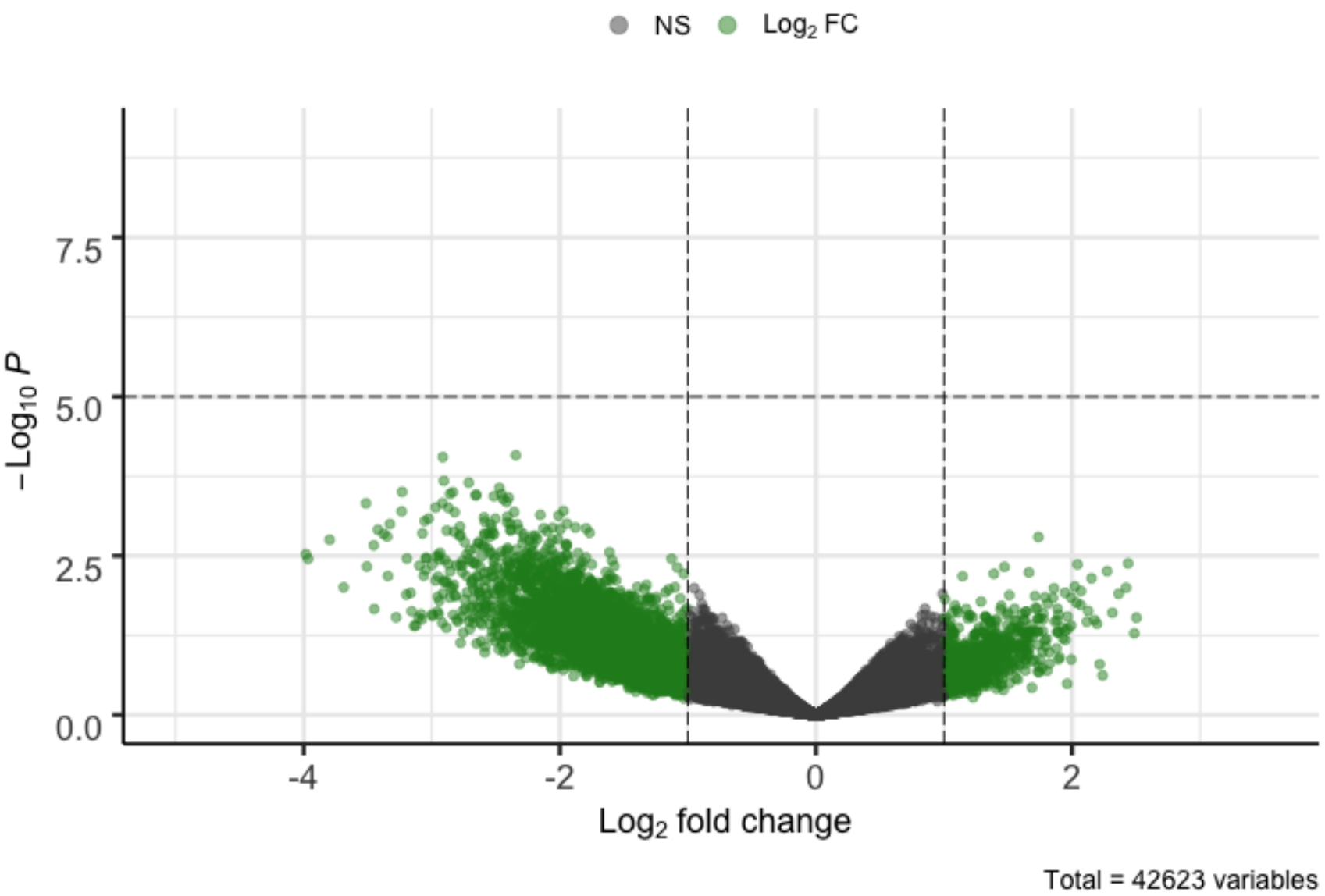
Diagnostic v. Relapsed Samples: Methylation Sites



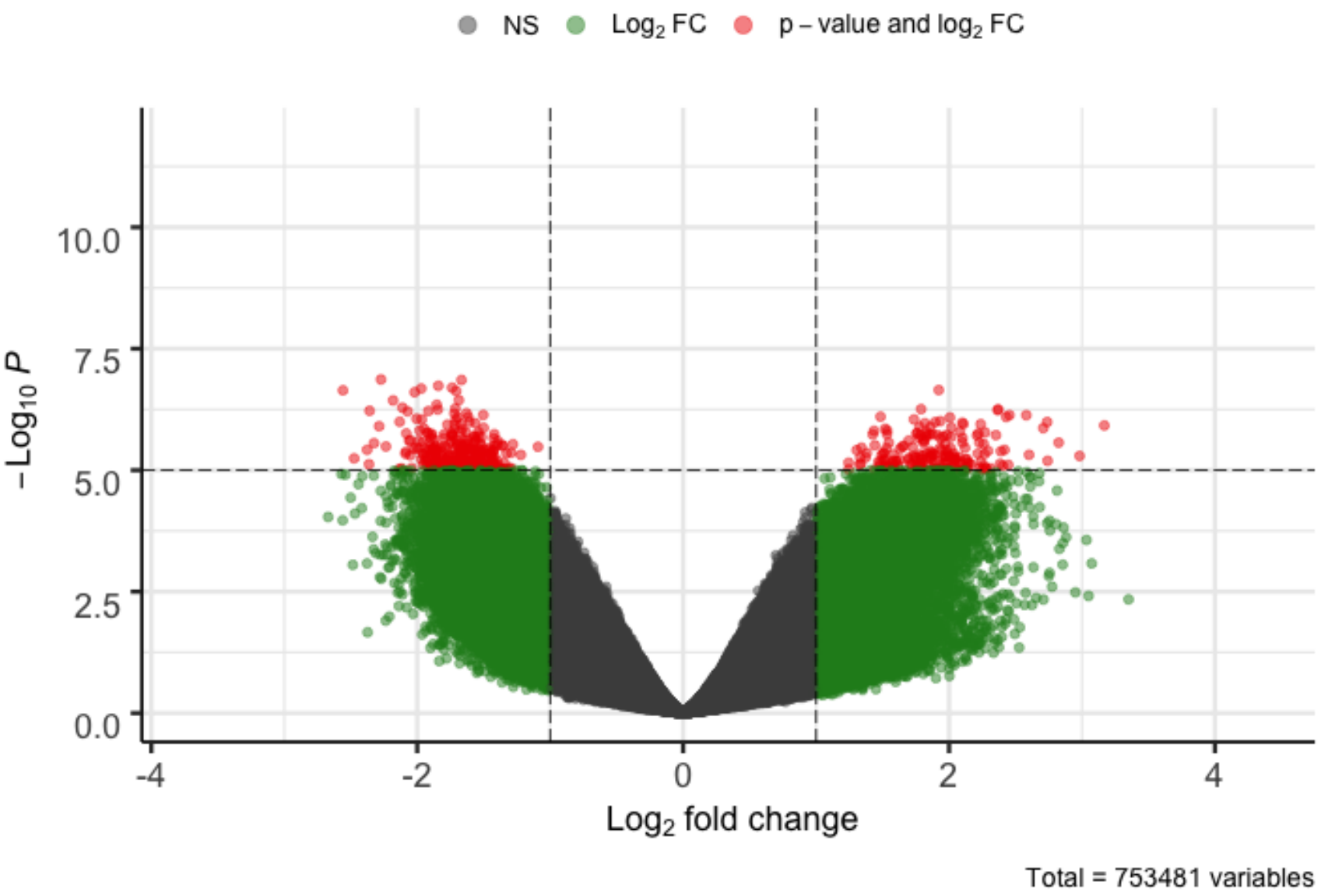
Diagnostic v. Relapsed Samples: Gene Network Analysis



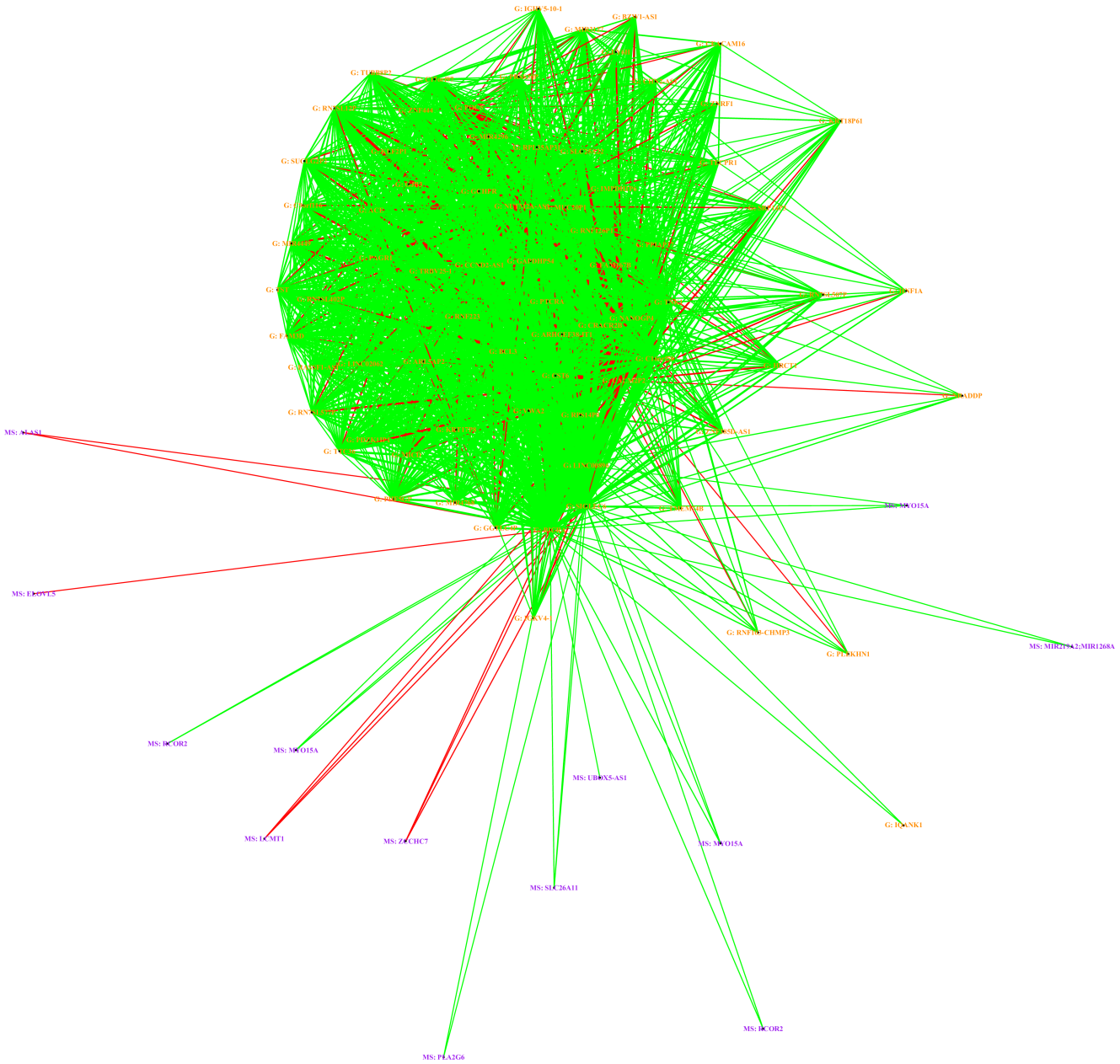
Diagnostic vs. Cured Samples: Gene Expression



Diagnostic vs. Cured Samples: Methylation Sites



Diagnostic vs. Cured Samples: Gene Network Analysis



SmCCNet identifies key DLBCL genes from literature

Gene	Function	OMIM	Citation
CREBBP	transcription factor	600140	Pasqualucci et al. (2011)
TNK1	tyrosine kinase	608076	May et al. (2010)
BCL3	NF-κB inhibitor	109560	Ibrahim et al. (2011)
ZCCHC7	TRAMP component	NA	Chong et al. (2018)

Conclusions

[INSERT CONCLUSIONS HERE]