BUILDING SEX-SPECIFIC SYNTHETIC LETHALITY NETWORK IN CANCER - TEMP NAME

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July 28, 2023

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Introduction/Background Information

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Building Pan-Cancer Synthetic Lethality Networks in a Sex Specific Manner

Materials and Methods

TCGA Data

RNA sequencing (RNA-seq) data was obtained from The Cancer Genome Atlas (TCGA). Raw STAR (Spliced Transcripts Alignment to a Reference) aligned counts for tumor tissue and healthy tissue samples were collected. The Cancer Genome Atlas contains genomic information which spans 33 cancer types. For the purpose of this study, only 12 of the 33 cancer types were considered. We first filtered out sex-biased cancers which include breast invasive carcinoma (BRCA), cervical cell carcinoma (CESC), ovarian serous cystadenocarcinoma (OV), prostate adenocarcinoma (PRAD), testicular germ cell tumors (TGCT), uterine corpus endometrial carcinoma (UCEC), and uterine carcinosarcoma (UCS). The reason for this was due to the fact that we are already aware of sex biases in these cancer types. Next, we filtered out blood cancers as well as cancers which lacked normal tissue gene expression samples. This included adrenocortical carcinoma (ACC), lymphoid neoplasm diffuse large b-cell lymphoma (DLBC), glioblastoma multiforme (GBM), acute myeloid leukemia (LAML), and brain lower grade glioma (LGG). The reason for this was due to the fact that we did not have adequate control samples to compare to tumor samples. Finally, we filtered out cancers that did not have any matching pairs of samples (NT and TP from same individual), as well as cancers that had less than 10 matched sample pairs across both males and females. This included mesothelioma (MESO), skin cutaneous melanoma (SKCM), thymoma (THYM), uveal melanoma (UVM), cholangiocarcinoma (CHOL), pancreatic adenocarcinoma (PAAD), pheochromocytoma and paraganglioma (PCPG), rectum adenocarcinoma (READ), and sarcoma (SARC). We selected matched tumor-normal sample pairs to help control for genetic background and other individual-specific factors that could influence gene expression. Once cancer types were selected, two pan-cancer raw count gene expression matrices were created, one for males and one for females.

Table 1: List of 12 TCGA Cancer Types With Number of Matched Tumor-Normal Samples in Males and Females.

TCGA information		
Cancer Type	Matched Female Samples	Matched Male Samples
BLCA	9	10
COAD	21	20
ESCA	5	8
HNSC	14	29
KICH	12	13
KIRC	20	52
KIRP	10	22
LIHC	22	28
LUAD	34	24
LUSC	14	37
STAD	10	23
THCA	42	17
TOTAL	213	283

Pre-filtering and Normalization of Raw RNA-seq Count Data

Raw count gene expression matrices for males and females were pre-filtered to remove genes unlikely to exhibit differential expression. For each matrix, we calculated the 90th quantile of overall gene expression as a threshold. For each gene in the matrix, we checked to see whether its expression was greater than the threshold in at least 1 sample. We removed genes where no samples showed an expression value greater than the quantile threshold.

The pre-filtered matrices were then normalized using the DESeq2 package in R (Love et al. 2014). RNA-seq data must be normalized in order to account for factors that prevent the direct comparison of expression measures. The DESeq2 package employs a median of ratios normalization method to account for the inherent biases associated with RNA-seq data. Both sequencing depth (# of reads generated per sample) and RNA composition (differences in composition of RNA molecules in a sample) are factors accounted for by the DESeq2 package. Raw counts are divided by size factors determined for each sample by computing the median ratio of gene counts relative to the geometric gene calculated per gene (Love et al. 2014). Figure 1 summarizes the effects of normalization for both male and female RNA-seq data. The distribution of counts across samples becomes much more consistent, thus making the samples comparable.

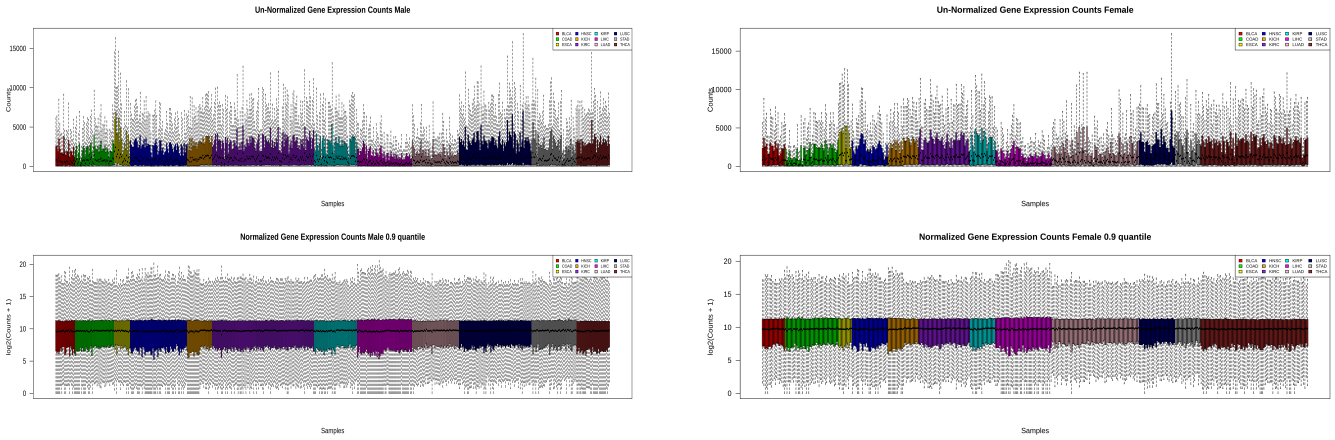

Figure 1: Boxplots highlighting the distribution of raw RNA-seq data (top row) vs normalized RNA-seq data (bottom row) in males (left) and females (right) across normal tissue and tumor tissue samples from 12 TCGA cancer types. Each colour represents a specific cancer type.

Data Quality Assessment (PCA, NPManova)

Once expression matrices were normalized

Differential Gene Expression Analysis with DESeq2

Results

Discussion

References

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