Comparative transcriptomic data can be used to examine similarities and differences in the gene expression of organisms or cells, which can be beneficial when trying to discover treatments for cancer or mental health diseases. Typically, two independent experiments are performed that each identify differences in gene expression between two experimental conditions. The differences are compared between experiments to test for significant overlap in differentially expressed genes. Traditionally, all genes are treated equal without taking into consideration that genes may have varying numbers of transcription factor binding sites, leading to different variability in gene expression and may overstate the degree of genetic overlap due to the simplifying assumption that all genes are equal. The purpose of this study was to create a computer simulation that considers varying numbers of transcription factor binding sites of genes and generates random gene expression profiles to generate a null expectation of transcriptome overlap for genes with different genetic architectures. When compared to empirical data, results suggested that traditional methods for measuring gene overlap may need to be reevaluated and more stringent criteria need to be applied when comparing transcriptomes. (Received September 20, 2015)