ANALYSIS OF ENDOCRINE INTERACTIONS AND SEX DIFFERENCES VIA TISSUE PAIR GENE EXPRESSION CORRELATIONS

THE SOCIETAL IMPLICATIONS OF ADOPTING CRISPR TECHNOLOGY

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By

Emmanuel Enoch Edu Jr.

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A SOCIOTECHNICAL SYNTHESIS

With nearly a quarter of deaths in the United States related to cardiovascular disease and over 26 million adults suffering from type II diabetes, researchers are encouraged to study the complex mechanisms involved in such illness to develop efficient therapies. Understanding the endocrine signaling pathways, and the downstream effects of gene expressions can be a powerful tool in the fight against prominent diseases. My technical research project improves the efficiency of gene expression analysis using bioinformatics, in an effort to provide researchers with more tools to better comprehend the human genome. This project may be of use to those within a lab setting but, there is room for this kind of research to produce results that the general population may benefit from. The knowledge of human gene expressions can be translated into human genome editing with the use of CRISPR/Cas9 technology. Human gene editing has the potential to mitigate, and in some cases remove, the presence of certain diseases and disorders. Though CRISPR has made reasonable progress in labs, significant safety and efficacy trials are needed before the new technology is released for clinical use. It is my belief that gene editing technology will succeed in these trials eventually, however the societal implications of this therapy remain to be discussed before the general public chooses to utilize it. Using the Social Construction of Technology (SCOT) framework, my STS paper discusses the societal factors involved in the adoption of human genome editing into the clinical space and advocates for its adoption.

Disease genetic heritability has led researchers to create computational models that map out gene expressions, and their downstream effects in neighboring organs, to better understand the communication pathways that lead to disease states. The project adapts from the work of Seldin et al. in 2018 that modeled the relationship of gene expressions in the endocrine system

within mice, and applies it to observe metabolic differences in the adipose tissue of men and women. This project resulted in the development of a R software package capable of identifying gene correlations between pairs of tissues. Identification of these correlations will be extremely applicable in the development of treatments for certain diseases like sickle-cell, lung cancer, and beta thalassemia. One research team even found that men and women have different fat distribution patterns that impact their risk for metabolic and cardiovascular diseases. Men store adipose tissue around their abdominal region, which leads to an increased risk for CVDs. In comparison, women store adipose tissue in the gluteofemoral region, and were found to have improved systemic metabolism to their male counterparts, despite having higher total body fat. These findings implicate a significant difference in adipose tissue function in men and women. Our research project builds upon analyses like the one mentioned previously by improving the efficiency of gene correlation analysis between tissues. This knowledge can enhance current approaches that treat patients based on broad assumptions that can be found to be ineffective at efficiently mitigating health complications.

The development of our R package utilized human tissue data sourced from the GTEx database on expression in 47 different tissue samples. Human RNA-seq gene expression data was properly annotated, negative log base 10 normalized, and quality controlled via R studio and JupyterLab notebook. Currently the R package is assembled for completing various tasks in data analysis including gene filtration based on variance percentage and produces a series of scatter plots and histograms based on a biweight midcorrelation analysis. This R package is publicly available on Github and is equipped with a vignette and manual for users to understand how to properly utilize the developed package.

The results of the project primarily reside in the functionality of the gene analysis R package. This project has several functions that allow the user to have many options on how they want their gene analysis to be conducted. There is a parameter to adjust for the most highly variable genes between tissue pairs, in order to examine which genes are the most highly correlated. The project uses this parameter as well as the correlation coefficients and p values of the biweight midcorrelation analysis to produce scatter plots with regression lines. It should be noted that the majority of the visualizations made by the package use liver and subcutaneous adipose tissue data. To ensure that the results are consistent across other tissue pairs, the analysis was also conducted using a stomach and subcutaneous adipose tissue pairing. It was determined that the efficiency of the package was not compromised when different tissue pairs were used. The software is in a state where it could conduct a sex differences analysis with relative efficiency, however our team did not have enough time to properly conduct an analysis credible enough to document and cite.

For my STS research paper I sought to understand the societal implication of adopting human gene-editing techniques into clinical settings. My thesis is to advocate for the adoption of CRISPR-Cas9 technology as a viable medical therapy. CRISPR technology is capable of inserting or deleting sequences of DNA from living cells with high precision. This caliber of augmentation can be utilized to develop a series of novel therapies to combat diseases like sickle cell disease and various cancers. Though the potential of this technology is revered, it cannot fully take form in mainstream society without government approval and the trust from the general public. This is why I conducted research to understand the entities and factors involved with introducing such a promising technology into the medical world.

To understand CRISPR's potential, researchers at several universities have already incorporated this technique into practice. One research group sought to incorporate the technology to combat HIV. University of California researcher, Yuet Kan, spearheaded a research study in 2014 which sought to use CRISPR technology to insert HIV-resistant genes within white blood cells. They found that the edited white blood cells were resistant to the virus, but further trials would have to be conducted for efficacy in an *in vivo* study. There have also been applications in cancer research. Oncologists at the Barts Cancer Institute published a review article detailing the use of CRISPR-Cas9 to expedite the development of oncolytic viruses, which are viruses that target cancer cells, and to evaluate its application in viral biology research. Another research group at MIT used CRISPR technology to cure mice suffering from a liver disorder by correcting the mutated gene. At the time this was one of the first research documents that proved the effectiveness of CRISPR-Cas9 to successfully cure an organism of disease. It is results like these that should give the people confidence to accept gene-editing technology.

The SCOT Framework used to analyze the factors involved with the adoption of CRISPR include gene labs, hospitals, government, and the public. All entities have a significant stake in its development and use but through my research, I argue that the public and the government have the most important roles. Since gene-editing is an area of science that is relatively new, it is imperative that those who preside over the people are held responsible for protecting the public. Additionally, for CRISPR to be an effective therapy it must garner the trust of the public in order for clinical trials to persist.

CRISPR technology continues to prove its worth through animal lab trials. If this technique develops to be safe for humans, then we can expect to receive a myriad of benefits

from this therapy in the future. The adoption of human genome editing requires cooperation from several entities: labs, hospitals/clinics, government agencies, and the public. Safety and efficacy can be accounted for through regulation, however the ethical and societal implications ought to be considered when making the shift towards commercial access. It may be found that a considerable amount of people are not ready for this kind of scientific advancement but that should not halt the process of approval. Rather the hesitation of the public should be used as a sign to evaluate the permissions and capabilities of CRISPR technology.

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