Astrid M Manuel

Innovating Drug Repositioning Strategies for Multiple Sclerosis via Translational Bioinformatics Approaches

Multiple sclerosis (MS) is an autoimmune disease in which immune-mediated demyelination of the central nervous system (CNS) leads to serious neurological deficits. Investigators postulate that MS is a genetically predisposed disease, onset after a suspected environmental trigger. Despite recent advancements in MS treatment, it remains that several patients still experience treatment-resistant MS. However, drug development is a time-consuming and risky process; on the other hand, drug repositioning strategies, which find new indications for existing drugs, have had higher rates of success and lower investment costs. We hypothesize that better understanding of the genetic risk factors of MS may aid to discover underlying biological pathways of MS pathology and to pinpoint potential repurposable drug candidates. The most recent and largest genome-wide association study (GWAS) of MS, which quantitatively measured the genotypes of MS cases and healthy controls, identified 233 genetic variants associated with MS with genome-wide significance. We use network-assisted methods to integrate this GWAS data with other disease-specific molecular (proteomic, transcriptomic and epigenomic) datasets to investigate the complex genetic architecture of MS. We pinpoint potential gene-environment interactions in MS and link genetic risk factors of MS to existing drug target genes. Based on the enrichment of drug target genes in MS-associated gene networks, we propose potential repurposable drug candidates for MS, including the leukotriene receptor antagonist montelukast, *HDAC1* inhibitor vorinostat, and *ELANE* inhibitor sivelestat. Currently, we are using administrative health claims data of the Optum UTHealth database to evaluate the potential clinical outcomes of these drug repositioning strategies.