1. Introduction

1.1 Background

Not all patients respond to drug therapy is in a uniform or a beneficial fashion. There are many variabilities in the human drug response. These differences between patients respond to drugs is affected by many factors, including their genetic and phenotypic traits. These traits in patients usually affect how their body absorbs to drugs, metabolites the drugs, or their response towards the effects of the drugs. Take an example among family members: some prescription can only be affected to one specific person inside the family. And due to the patients variability of drug response, doctors must carefully choose and adjust the dosage of appropriate drugs for each prescriptions. This process would be even more complicated if the person prescribed another medication and/or has another disease; due to the drug-drug or drug-diseases interaction (Lynch, 2017).

One of the fundamental steps of having a clear view of differences in the human drug response is by the study of pharmacogenomics. Pharmacogenomic studies how medicine interacts with the inherited genes, which caused the effect of a specific individual's drug responses (Understanding Pharmacogenomics, 2018). It is a relatively new field in science which combines both pharmacology and genomics. We believe that this fundamental step may lead us to develop a treatment of tailored drugs for any healthcare problems.

One of the examples of pharmacogenomics is genetic association studies. The genetic association occurs when a genotype or more than one genotypes of the same population with a particular phenotypic trait are present more often than expected by the chance occurrence (Cathryn M. Lewis, 2012). For this manuscripts, we chose the human UGT1A gene as our targeted genes since it is likely to be significantly contributed in the improvement of drug efficacy. Not only that this gene shows a responsibility in the ethnic diversity due to their genetic variability, the exposure regarding the genetic variants inside UGT1A

gene cluster has yet been discovered (Strassburg CP, 2008). This study aims to study the correlation between the genetic variation in the candidate genes to identify regions that could possibly contribute in a specific drug response.

The genetic variation of each's drug response is mainly due to the presence of single nucleotide polymorphisms. Single nucleotide polymorphisms, abbreviated SNPs, are the most common biomarkers to see the genetic variation among individuals. Each SNP represents a difference in the nucleotide. When SNPs occur within a gene or in the regulatory region, they may play a more direct role in disease by affecting the gene's function. It will also show that the gene has more than one allele. Moreover, SNPs may lead to the variations in the amino acid sequence, which will be translated differently from each individual and give the different effects in the gene later on.

Although some particular SNPs may not have any effect on health or diseases, we still presume that SNPs can act as biological markers to help scientists locate genes that are associated with the disease. Some studies have also found SNPs that may help predict an individual's response to certain drugs, susceptibility to environmental factors, and risk of developing particular diseases (Single-nucleotide polymorphism, 2018). In short, we suspect that the higher frequency of a single-nucleotide polymorphism (SNP) allele or genotype in a series of individuals increases the risk of having a particular drug response.

In the past, DNA sequencing methods were used to study the gene association and locate the SNPs. As time goes by, researchers found an easier way to implement this testing methodology. Today, genes can be studied directly using whole genome sequencing (WGS) and whole exome sequencing (WXS) (Cathryn M. Lewis, 2012). Here, we used the whole genome sequencing data to identify SNPs that are present inside statin-treated patients of Singaporeans population. We apply this method to search for the common variants that occur more frequently in people with a particular drug response than in those people without any side effects (case-control). But due to the limited amount of time, this manuscript will

only be limited to a specific region in the gene of interests; UGT1A Genes. Hopefully, this particular study could be beneficial for further implementation of precision medicine.

1.2 Objective

Nowadays, polymorphisms play an essential role in biological research. To verify the importance of polymorphisms in human drug response, genetic association study was applied to study a cohort of patients taking statin treatment. Statin has been proven as the most widely prescribed drugs to help lower cholesterol levels in the blood. However, although statins are both practical and generally safe, some of the patients might some might have not compatible of using statin or might have experienced the side effects of statins. The side effects include muscle pain, increased the risk of diabetes mellitus and even abnormalities in liver enzyme tests. Some studies mentioned that up to 10% until 15% of statin-treated patients, experience myalgia syndrome ranging in severity from mild to moderate muscle pain (myalgia) to severe and even-life threatening myopathies. In these rates, they are much higher than those seen in randomized clinical trials. These are the most frequent reason for the discontinuation of statin therapy. But unfortunately, the mechanisms underlying statin myalgia are still not well understood (Elam MB, 2017).

Apart from the side effects, the rate of drug metabolism can also be fundamentally varied within different patients. This affects the efficacy of drugs towards patients who have either high or low metabolism rates. For example, those with high metabolites level clear the drug very quickly and the concentration of the drug might not be reached at certain levels (Yolanda Smith, 2019). This study speculated that the presence of certain polymorphisms is responsible for the variety of patient's drug response. Hence, the objective of this study is to apply genetic association to associate the phenotype and genotype of patients consuming statins in order to identify SNPs that are associated with the side effects of statin and the level of the metabolites of statin. We hope to discover some potentially functional SNPs

as biomarkers for predicting population differential response to drugs. We hoped that these genetic differences will be useful to predict which medication is more effective for a particular group and hopefully help to prevent adverse drug reactions (What is pharmacogenomics?, n.d.).

1.3 Hypothesis

The study hypothesized that the polymorphisms or variants presence in UGT1A Genes could affect the drug response of the patients undertaking statin therapy.