Chapter I

INTRODUCTION

1.1. Background

The International Diabetes Federation (2021) reported that 415 million people have type 2 diabetes mellitus (T2DM), with the number predicted to climb to 642 million by 2040. Currently, India leads in the second-highest number of diabetic patients (74 million cases in 2021) and will account for over 20% of the global diabetic population by 2025 (Mohan et al., 2005; Vimaleswaran, 2020). The increased prevalence of T2DM among Asian Indians is recognized due to the South Asian or Asian Indian phenotype. The Asian Indian phenotype contributes to greater visceral or total abdominal fat, such as accumulated in waist circumference compared to Caucasians of the same age, gender, and Body Mass Index (BMI) (Alsulami et al., 2021; Sattar & Gill, 2015). In addition, Asian Indians tend to have larger waist-to-hip ratios (WHR), higher levels of plasma insulin concentrations, insulin resistance, and impaired pancreatic β-cell functions (Alsulami et al., 2021; Prabu et al., 2015). Moreover, the lipid profile of Asian Indians is distinctly characterized by decreased high-density lipoprotein (HDL) and increased small dense LDL (sdLDL) and triglyceride (TG) levels (Ganesan et al., 2011). Furthermore, Asian Indians are known to have an imbalanced dietary pattern, including lower in unsaturated fats (monounsaturated fatty acids (MUFA) and omega-3 polyunsaturated fatty acids (n-3 PUFA)), plant protein sources, and fiber, and higher in calories, refined carbohydrates, and saturated fats (Chandra et al., 2014; Gulati & Misra, 2017).

One of the important determinants of T2DM is dyslipidemia, an abnormality in lipid metabolism and a well-established heritable risk factor. Dyslipidemia is characterized by lowered HDL and raised LDL (particularly sdLDL), TG, and total cholesterol levels (Al-Bustan et al., 2018; Hirano, 2018; Luo et al., 2017; Matsuzaka & Shimano, 2020; Musunuru et al., 2012), which is comparable to the poor lipid profile found among Asian Indians (Ganesan et al., 2011). It is known that T2DM is caused by a multifactorial matrix of genetic and environmental factors that interrelate with one another (Zheng, Ley & Hu, 2018). Environmental factors such as unhealthy eating habits are known to amplify the risk of dyslipidemia and plasma lipid concentrations (Mirmiran et al., 2017; Rafiq et al., 2012). Moreover, evidence suggests that plasma lipid concentrations are influenced by the whole diet, quality, and quantity of the consumed dietary macronutrients (Jebb et al., 2010). However, the extent of these dietary responses varies between individuals due to genetic variations known as single nucleotide polymorphisms (SNPs) (Friedlander et al., 2000). Elsamanoudy et al. (2016) & Mirmiran et al. (2017) suggested that the understanding of SNPs as a risk factor for diverse

nutritional responses might reveal a better knowledge of the mechanisms through which diet influences lipid metabolism and subsequently T2DM risk. Kurano et al. (2016) and Pirim et al. (2014), also stated that the discovery of novel genetic loci and variations linked to plasma lipid metabolism when an individual consumes certain diets is becoming an interest for researchers to aid in disease risk assessment, diagnosis, and prognosis.

The genetic makeup of all humans is 99.9% identical, and the remaining 0.1% imparts an individual's distinctiveness and provides crucial information in regard to disease etiology (Ku et al., 2010). Several studies have discovered that SNPs in lipid and lipoprotein metabolism act as biomarkers of T2DM (Ahmad et al., 2019; Atanasovska et al., 2015; Consortium et al., 2015; de Waard et al., 2019). Besides, knowing that T2DM heritability ranges from 26% to 69%, pushes the quest for T2DM genetic predictors (Läll et al., 2017). The genes encoding for cholesteryl ester transfer protein (CETP) and lipoprotein lipase (LPL) have been demonstrated as novel genetic markers in genome-wide association studies (GWAS) and candidate gene studies correlated with multiple diseases and lipid traits in overall plasma lipid metabolism (Al-Bustan et al., 2018; Musunuru et al., 2012; Park et al., 2021; Pyun et al., 2012). The LPL gene is a rate-limiting enzyme that hydrolyzes circulating plasma TG-rich lipoproteins, present in VLDL and chylomicrons, into NEFA (non-esterified fatty acid) and 2-MAG (monoacylglycerol) to facilitate cholesterol transport, tissue metabolism, and HDL synthesis (Al-Bustan et al., 2018; Pirim et al., 2014). On the other hand, the CETP gene facilitates reverse cholesterol transport by exchanging the net movement of cholesteryl esters (CE) from HDL to atherogenic apoB lipoproteins-containing TG (Ilanbey et al., 2020).

The role of LPL and CETP SNPs in lipid traits and modulating their concentration is well established, however, it varies greatly between populations (Al-Bustan et al., 2018; Bangladesh et al., 2019; Musunuru et al., 2012; Park et al., 2021). Huang, Shu & Cai (2015) mentioned that 15% of all SNPs are population-specific, while nearly 85% are common across populations. It infers that a common allele is strongly correlated to disease and more likely to be found across populations. Nevertheless, different ethnic groups have varying gene frequencies, causing disparities in disease prevalence (Huang, Shu & Cai, 2015). In accordance with that, Braun et al. (2012) remarked that replication across ethnic groups is of importance to uncover ethnic-specific SNPs that contribute to different dietary responses. Notably, most of the gene-phenotype, gene-disease associations, and nutrigenetic studies have primarily been conducted among Americans (Ma et al., 2014; Rudkowska et al., 2013), Caucasians (Ma et al., 2014; Perrone et al., 2022), and East Asian populations (Hsu et al., 2019; Zhu et al., 2014). However, these findings have been inconsistent in terms of study designs, such as the use of genotyping and nutritional measurement, population stratification, and complex

polygenic factors of SNPs (i.e., multiple genes involved) in metabolic responses to the diet (Al-Bustan et al., 2018; Mirmiran et al., 2017). Given the abundance of studies from other populations, it remains uncertain whether the current nutrigenetic study in Asian Indians was thoroughly conducted.

1.2. Research Questions

1. What lipid traits are associated with LPL and CETP gene variations in Asian Indians, and how do the lipid concentrations vary?
2. What are the associated outcomes of LPL & CETP polymorphism and lipid traits when interacting with dietary factors in Asian Indians?

1.3. Objectives

The purposes of this review are as follows:

1. To explore the association between LPL & CETP gene variations and lipid traits (HDL, LDL, TG, and total cholesterol) in Asian Indians,
2. To investigate the interaction of LPL & CETP gene polymorphisms and dietary factors on lipid traits among Asian Indians, and
3. To examine the current public guidelines on certain dietary intake observed among Asian Indians, as well as the future outlook of nutrigenetic studies.

1.4. Scope of Work

The author's scope of work comprises as follows:

1. Online coursework (i.e., covering the topics of gene structure and regulation, gene discovery methods in genetic epidemiology, nutrigenomics and nutrigenetics, personalized nutrition, critical appraisal, introduction to bioinformatics tools, and population genetics) and data analysis training encompasses descriptive statistics, independent samples t-test, One-Way ANOVA, Chi-square test, linear and logistic regression analysis that were prepared for the second scope of work. The study was reported in the 7th-semester internship report titled "Training on Nutrigenetics, Personalized Nutrition, and Statistical Genetic Analysis at The University of Reading, United Kingdom".
2. Assist data analysis of a Ph.D. student nutrigenetic project from the University of Reading in December 2021 using SPSS software version 25. The goal of the study was to use a nutrigenetic approach to investigate the interactions between LPL and CETP genetic risk scores and dietary factors on lipid- and obesity-related outcomes in healthy and T2DM Asian

Indian adults. The article of this work titled “Impact of Lipid Genetic Risk Score and Saturated Fatty Acid Intake on Central Obesity in an Asian Indian Population”, authored by Ramatu Wuni, Evelyn Adela Nathania, Ashok K. Ayyappa, Nagarajan Lakshmipriya, Kandaswamy Ramya, Rajagopal Gayathri, Gunasekaran Geetha, Ranjit Mohan Anjana, Gunter G. C. Kuhnle, Venkatesan Radha, Viswanathan Mohan, Vasudevan Sudha, and Karani Santhanakrishnan Vimaleswaran. The article was published in the MDPI Nutrients journal: section of nutrigenetics and nutrigenomics, volume 14, issue 13, the year 2022, page 2713, doi: https://doi.org/10.3390/nu14132713.

3. Literature reviews on the published nutrigenetic studies examining the association between LPL and CETP genetic variants on lipid traits and the interaction of those genes with dietary factors on lipid outcome emphasizing the Asian Indian population. This thesis report focuses on this scope.

1.5. Benefits of Study

The following are some of the benefits of the study's findings:

1. Provide an update on the nutrigenetic (LPL and CETP gene x diet) research that has been published on Asian Indians. This highlights the LPL and CETP risk variants that influence the types and concentration of lipid traits when interacting with dietary factors.
2. Provide supplementary literature or as references for future nutrigenetic studies to validate the existing findings and delve into personalized nutrition approaches based on the genetic risk possessed among Asian Indians.