# CHAPTER I

# INTRODUCTION

## 1.1 Background

High density lipoprotein cholesterol (HDL-C) is the densest and smallest lipoprotein found in circulation. HDL-C particles consist of a hydrophobic core of the cholesterol esters and triglycerides which surrounded by a monolayer phospholipid, unesterified cholesterol and apolipoprotein (apo).[1]

One of the proposed atheroprotective functions of HDL-C is the process of reverse cholesterol transport (RCT), where cholesterol from peripheral is being removed, then preventing foam cells from developing into an atherosclerotic plaque.[2] Low level of HDL-C is associated with elevated risk of death due to coronary artery disease (CAD).[3] In patients with CAD, low level of HDL-C (less than 40 mg/dl) is the most common lipoprotein abnormality found (30-50%).[4] Low level of HDL-C along with high cholesterol concentration are also associated with an increased risk of Alzheimer disease.[5]

The prevalence of low HDL-C level is vary in several countries. Indonesian population has a prevalence of low HDL-C level about 43.6% for men and 57.8% for women.[6] Korean population has a prevalence of low HDL-C level about 23.8% for man and 47.5% for woman.[7] Meanwhile, it was estimated that approximately 25% of men in the UK were having low HDL-C level.[8] A study conducted at the Cipto

Mangunkusumo Hospital Jakarta Indonesia showed that the atherogenic lipid was commonly found in patient with low HDL-C level.[9] However, there is no data about genetic base of low HDL-C level.

The factors which have effect of low HDL-C level may be monogenic, polygenic, enviromental factor, and interactions between genetic and environmental factor.[2] Those environmental factors are gender, age, obesity, smoking, alcohol consumption, diet, physical activity, medications (such as steroids, niacin, statins and fibrate class), and metabolic disorders (such as insulin resistance and hepatic disease).[10,11] Based on the family studies and twin studies, 40-60% subjects with low HDL-C level in plasma seems to have a strong tendency to be inherited.[2] The low HDL-C level with monogenic causes is also described, although it is rare (less than 1%) and it only explains the cause of low HDL-C level in general population.[12] Low HDL-C level can be caused by several gene mutations such as *APOA1* gene mutation[13] which has important role in HDL-C metabolism.[14]

Apolipoprotein A1 (*apoA1*) is a major protein component[15] of HDL-C which is up to 70%.[16, 17] It plays a role as cofactor for lecithincholesterol acyltransferase (LCAT), substrate for scavenger receptor class B member 1 (SR-B1).[18] In the structure of HDL, apoA1 is the two groups of proteins which arranged in an anti-parallel double-belt structure.[19] ApoA1 protein is encode by *APOA1* gene which is located in chromosome 11q23.[13] *APOA1* spans about 2.2 kb and contains 4 exons.[20] Deletions in the *APOA1* result in low levels of HDL-C.[17] The monogenic disorder caused by *APOA1* mutation comprises about less than 5% of low HDL-C level

cases,[21] but it shows more acceleration in atherosclerosis process than other gene mutation which encode the main protein of RCT.[22] The risk of CAD caused by *APOA1* mutations is the highest among when it is caused by other gene mutations.[22]

Mutation of *APOA1* has never been reported in Indonesian subjects. This study identified *APOA1* gene variants in subjects with low level of HDL-C who visit Dr. Kariadi Hospital by using HRM technique. The technique is fast, sensitive and cost effective to detect mutation by differentiating the melting point.[23]

## 1.2 Research Question

### 1.2.1 General Research Question

Is there any predicted pathogenic mutation in *APOA1* genes in subject with low level of HDL-C?

### 1.2.2 Specific Research Question

1. Is there any genetic variation of *APOA1* gene in subject with low level of HDL-C?
2. How is the distribution of variant alleles *APOA1* gene in subjects with low HDL-C level.
3. Is the identified genetic variant of *APOA1* gene predicted to be pathogenic?
4. Is there any association of HDL-C level and the environmental factors?
5. Is there any association of *APOA1* variant and HDL-C level?

## 1.3. Research Purposes

### 1.3.1 General Purposes

To identify the predicted pathogenic mutation of *APOA1* genes in subject with low level of HDL-C.

### 1.3.2 Specific Purposes

1. To identify the genetic variation of *APOA1* genes in subject with low level of HDL-C.
2. To identify the distribution of variant alleles *APOA1* gene in subjects with low HDL-C level.
3. To identify whether the identified genetic variant gene is predicted to be pathogenic or not.
4. To identify the association of HDL-C level and the environmental factors.
5. To identify association of *APOA1* variant and HDL-C level.

## 1.4 Research Benefit

The benefit of this study is to provide information about mutation of *APOA1* gene in subjects with low level of HDL-C which may important for clinical management of patient with low HDL-C level.

## 1.5 Originality

This is the first study to identify *APOA1* gene mutation in Indonesian subjects with low HDL-C level. Table 1 shows the previous studies about identification of mutation in *APOA1* gene.

**Table 1.** List of previous studies about identification of *APOA1* gene mutation

| No | Author | Title of Publication | Method | Result |
|---|---|---|---|---|
| 1. | Haase CL, Frikke-Schmidt R, Nordestgaard BG, Kateifides AK, Kardassis D, Nielsen LB, *el al.* (2011, Journal of Internal Medicine) | Mutation in *APOA1* predicts increased risk of ischemic heart disease and total mortality without low HDL-C levels. | Resequence *APOA1* gene and examine the effect of mutation on HDL-C level, risk of IHD, MI and mortality. | A164S on *APOA1* gene predicts an increase of IHD, MI and total mortality without low HDL-C level. |
| 2. | Dodani S, Dong Y, Zhu H, George V. (2008, Indian Journal of Human Genetics) | Can novel *APOA1* polymorphisms be responsible for low HDL in South Asian immigrants? | DNA sequencing of *APOA1* gene then associated with the level of HDL-C, total cholesterol and LDL-C. | C938T has significant association to HDL-C levels, total cholesterol and LDL-C levels. |
| 3. | Shioji K, Mannami T, Kokubo Y, Goto Y, Nonogi H, Iwai N. (2004, J Hum Genet) | An association analysis between *APOA1* polymorphisms and the high-density lipoprotein (HDL) cholesterol level and myocardial infarction (MI) in Japanese. | Sequencing to find *APOA1* gene polymorphism then associated with the HDL-C level and myocardial infarction incidence. | Nine polymorphisms in *APOA1* gene. The *APOA1* 84T/C polymorphism has the greatest effect on the HDL-C level and may be a new risk marker. |