CHAPTER ONE

INTRODUCTION

1.1 Background of Study

Cardiovascular disease (CVD) is a collective term for all diseases affecting the heart, arteries and blood vessels which include coronary artery disease (CAD), stroke, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis and pulmonary embolism. CVD is the leading cause of mortality and primary contributor to the burden of disease worldwide (Murray & Lopez, 1997; Lopez *et al*., 2006). World Health Organization (WHO) in 2004 estimated almost 17.1 million people around the world die of CAD and stroke, the two major manifestations of CVD. Of these deaths, 7.2 million deaths were due to CAD and 5.7 million were due to stroke. Between 1990 and 2020, mortality from CAD in developing countries is expected to increase by 120 % for women and 137 % for men (Murray & Lopez, 1996; Leeders *et al*., 2004). According to WHO report in 2002, CVD accounted for 30 % of all death in Malaysia (Figure 1.1).

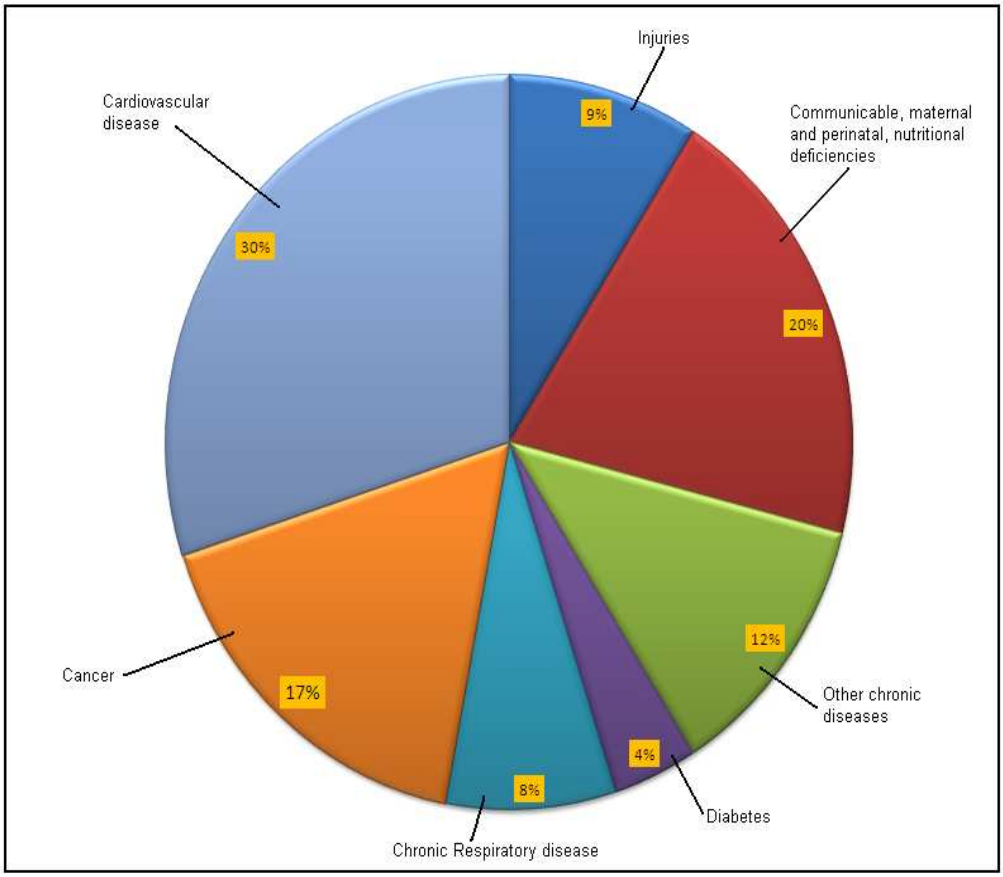

Figure 1.1: Death by causes in all ages among Malaysians in 2002 (World Health Organisation, 2002).

In 2004, Zambahari reported that CVD is the principal cause of admission and death in government hospitals in Malaysia. Of these CVD admissions and deaths in government hospitals from 1985 until 2000, CAD accounted for 25% to 33% of admissions and 27% to 35% of death (Zambahari, 2004). The development of CAD is influenced by a number of risk factors. Among the conventional risk factors are age, gender, smoking habit, systolic blood pressure (BP), total cholesterol (TC) and high density lipoprotein (HDL) (Khot *et al*., 2003). These risk factors are classified into modifiable and non-modifiable factors (Table 1.1).

Table 1.1: Modifiable and non-modifiable coronary risk factors (adapted from Black, 1992).

Cardiovascular Risk Factors	
a) Non-modifiable Risk Factors	b) Modifiable Risk Factors
1. Age 2. Gender 3. Hereditary	1. High blood pressure 2. Elevated blood lipids 3. Lipoprotein (a) 4. Physical inactivity 5. Cigarette smoking 6. Obesity 7. Glucose intolerance 8. Diabetes 9. Fibrinogen 10. Left ventricular hypertrophy 11. Cocaine 12. Behavioural factors (stress, Type A personality)

High prevalence of coronary risk factors among rural communities in Malaysia was reported by Nawawi *et al*., (2002) and Zambahari (2004) stated that the National Health and Morbidity survey showed 61% of Malaysian population had one coronary risk factor or more. High level of serum cholesterol or hypercholesterolaemia is a major risk factor for the development of CAD (Grundy & Vega, 1990). Hypercholesterolemia is typically caused by fat-rich diet and unhealthy lifestyle, combined with problems of inefficient ability to regulate fat metabolism.

Hypercholesterolaemia can be divided into primary and secondary causes. Secondary causes are more common which include hypothyroidism, nephrotic syndrome, cholelithiasis, and certain drugs such as thiazides and corticosteroids. Primary causes of hypercholesterolaemia are due to underlying genetic disorders such as familial polygenic hypercholesterolaemia and familial hypercholesterolaemia (FH).

FH was first described in 1920 (Burns, 1920) and is one of the commonest single gene disorders. Based on World Health Organisation (WHO) consultation report on FH, the condition has been identified as one of the most relevant genetic diseases (WHO, 1999). FH is inherited as a monogenic autosomal co-dominant trait (Khanchadurian, 1964). The affected individuals have a defect in the low-density lipoprotein receptor (LDLR) which leads to the accumulation of low-density lipoprotein cholesterol (LDL-c) in plasma (Goldstein and Brown, 1973; Goldstein & Brown, 1974; Brown & Goldstein, 1986). The prevalence of heterozygous FH in most western population is estimated to be 1 in 500 (Goldstein *et al*., 1973; Heath *et al.*, 2001) while prevalence of more severe homozygous FH is 1 in 1 million (Khanchadurian & Uthman, 1973).

Clinically, FH is characterized by substantial increased levels of total cholesterol, two to threefold elevation of LDL-c levels and presence of tendinous xanthomata (Goldstein *et al*., 2001). Whilst FH heterozygous are more prone to premature CAD (van der Graaf *et al*., 2009), homozygous individuals are more severely affected and may die before reaching maturity (Allen *et al*., 1980).

FH is a treatable inherited disease and preventive measures can be taken and intensified, including pharmacotherapy to prevent morbidity and mortality due to CAD. The diagnosis of FH is made based on the total cholesterol and LDL-c levels combined with clinical examination and family history. Currently, genetic testing for mutations in LDLR genes is not routinely available. Reliable screening and definitive confirmatory methods are important in the family screening and diagnosis of these potentially treatable and preventable complications of FH. With the advancement in molecular screening methods combined with confirmatory DNA sequencing, it is hoped that these strategies are able to contribute to early and accurate diagnosis, thus the management can be initiated earlier to prevent the FH complications.

1.2 Objectives of Study

The objectives of this study were

i) to screen for mutations in all 18 exons and promoter region of low density lipoprotein receptor (LDLR) gene among patients with familial hypercholesterolaemia.

ii) to characterise the types of mutations in the LDLR gene among patients with familial hypercholesterolaemia.

1.3 Significance of the study

The prevalence of FH and the different type of mutations in Malaysia is still unclear and poorly characterised. Extrapolating the prevalence of heterozygous FH in Western populations into Malaysia population of about 25 millions, it would be estimated that about 50 000 Malaysians would be affected and at risk of developing premature CAD. However, most FH patients remained undiagnosed or diagnosed after their first coronary event (Marks *et al*., 2000). Maximum health benefit and prevention of mortality and morbidity are possible in FH patients if they are identified at young age and treatment is initiated as early as possible.

The identification of disease-causing mutations in LDLR gene is usually done by DNA sequencing but the cost is high and thus, not offered routinely. With the development and optimisation of screening method using denaturing high performance liquid chromatography (DHPLC), the cost of identifying the LDLR gene mutations causing FH is expected to be lower and affordable. The diagnosis of FH with proper family history, clinical examination and measurement of serum total cholesterol and LDL-c levels, combined with genetic screening and confirmatory methods are expected to contribute to better patient management to prevent atherosclerosis-related complications of FH.

This project will form an advanced move for the development of molecular biology techniques in the field of lipid disorders especially in primary hypercholesterolaemia. Once established, this specialised service can be offered at national and regional levels. This will further enhance the quality and efficiency of patient care, preventive medicine and counselling services to this potentially treatable case of primary

hypercholesterolaemia in terms of reducing morbidity and mortality from premature atherosclerosis-related complications.