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Review

Single nucleotide polymorphisms of microRNA in cardiovascular diseases

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ABSTRACT

Despite the advances in medicine and in science of diagnosis, cardiovascular diseases (CVD) remain the number one cause of morbidity and mortality worldwide. Apart from the modifiable risk factors, genetic factors are believed to also influence the outcome of this umbrella of diseases. Under the genetic factors, miRNA polymorphisms, namely miR-146a (rs2910164), miR-196 (rs11614913) and miR-499 (rs3746444), have become an important tool to study the mechanism that underlie the pathogenesis of this disease. In this review, we analyze the advances made through various research studies and the evidence provided by them in the area of miRNA polymorphisms by comparing the allelic frequencies and genotyping patterns. Interestingly, these studies have contradicting results even those conducted in same set of population. We also highlight the gap in literature search as majority of these studies have been conducted in Chinese population and data gaps are evident in Caucasian population, along with developing countries like, India, where no such data is available. This makes the daunting task of presenting a global picture and of the extent these polymorphisms play a role in CVD progression, even more difficult. Therefore, we suggest that more work needs to be done by taking various geographical domains in to consideration. Also, larger sample size calculated through statistical tools is the key to progress in establishing the genetic co-relation of miRNA polymorphisms and CVDs.

1. Introduction

Cardiovascular diseases (CVD) remain the leading cause of mortality and morbidity in both developed and developing nations, despite the scientific advances in disease prevention, diagnosis and treatment [1]. CVD is a group of disorders associated with heart and circulatory system blood vessels, including coronary artery disease (CAD), cerebrovascular disease, rheumatic heart disease, Congenital Heart Disease (CHD) among others [2,3]. The high global prevalence of CVD makes it important to understand the genetic factors involved. Understanding the association of these genetic factors, such as single nucleotide polymorphisms (SNPs) along with environmental factors, is important for a better understanding of CVD mechanism at genetic level.

The present review aims to discuss the association of microRNAs (miRNA) SNPs with CVDs. The review will also discuss how the SNPs at miRNA level differ from genomic DNA polymorphism. It is important to understand how the two differ from each other because of an emerging role of miRNA SNPs in cardiovascular disease profile. The review will also summarize the research carried out in the form of association studies exploring the relationship between miRNA SNPs and CVDs, till the time this article is written.

1.1. Prevalence

According to WHO-NCD burden report (2014), CVD is the leading cause of non-communicable disease (NCD) deaths worldwide (17.5 million or 46.2% of NCD deaths) [4]. World Health Report (2016) stated that 37% of premature deaths occur due to CVDs. Alcohol consumption causes highest number of deaths due to CVDs as compared to its contribution to other disease mortalities. According to a report by European Heart Foundation, each year CVD causes over 4 million (47%) deaths in Europe, accounting for 52% deaths in women and 42% deaths in men. Prevalence of CVD (including coronary artery disease, heart failure, stroke, and hypertension) in adults (both men and women) indicated that the prevalence of CVD increases with age [5].

1.2. Risk factors

Valtorta et al., showed that study subjects with poor social relationships had 29% increased risk of Coronary Heart Disease (CHD)

Abbreviations: PCR-LDR, polymerase chain reaction-ligation detection reaction; HRM, high-resolution melting-curve analysis; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; CHD, Congenital Heart Disease; DCM, Dilated Cardiomyopathy; CAD, Coronary Heart Disease; CR, Coronary Restenosis; MI, Myocardial Infarction; ACS, Acute Coronary Syndrome; AMI, Acute Myocardial Infarction

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Table 1
miRNA polymorphisms associated with CVD.

miRNA	SNP ID	Alleles	Chromosome	Location of miRNA	Site of polymorphism	Reference
miR-146a	rs2910164	C/G	5	Chromosome 5	G-U pairing → C-U mismatch stem structure of pre-miRNA on human chromosome 5	de Aguiar Vallim et al. [72]
miR-196a2	rs11614913	C/T	12	Chromosome 17	Stem region opposite the mature miR-196a2 sequence/corresponding 3p mature miRNA region	Bastami et al. [35]
miR-499	rs3746444	A/G	20	Intron of Myh7b	Stem region opposite the mature miR-499 sequence. A-U pair → G-U mismatch in the stem structure of miR-499	Sung et al. [63]
miR-149	rs71428439	A/G	2	Chromosome 2	Stem region outside the mature miR-149 sequence and changes the structure of the miR-149 precursor	Zhao et al. [69]
miR-218	rs11134527	A/G	5	Chromosome 4	Putative promoter region of pre-miR-218	Smith et al. [70]
miR-423	rs6505162	A/C	17	Chromosome 17	premiRNA region of miR-423	Ghanbari et al. [71]
miR-4513	rs2168518	C/T	15	Chromosome 15	A seed region variant of miR-4513	Zanetti et al. [41]

incidence [6]. According to World Heart Federation, the risk factors associated with CHD and stroke are family history, ethnicity and age of an individual [5]. These are non-modifiable risk factors. However, risk factors such as tobacco consumption, high blood pressure, obesity, lack of physical exercise, diabetes, alcohol consumption and diet high in fats can be modified. People who belong to a lower income group are also more susceptible to cardiovascular disease risk [7,8]. The World Health Report (1999) estimated that in the year 1998, 78% NCD burden and 85% of the cardiovascular diseases (CVD) burden arose from the low and middle income countries [9]. The risk factors for CVD in India include, alcohol consumption, tobacco use and hypertension [10]. According to World Heart Federation reports, upon comparing the prevalence of modifiable risk factors such as smoking, alcohol consumption, obesity etc. between developed and developing nations, similar trends can be followed, indicating that modifiable risk factors may pose similar effects on different populations across continents [5]. Having said that, fat consumption, physical activity etc. do vary among different countries due to marked difference in lifestyle and cultural practices.

2. microRNA

MicroRNAs (miRNAs) are a class of non-coding, small (20–23 nucleotides in length), single-stranded RNA molecules. miRNA regulate gene expression at post transcriptional level in both healthy and diseased state [11,12]. Single nucleotide polymorphisms (SNPs) are the variations in DNA at nucleotide level. According to miRBase, a total of 1881 miRNA sequences (GRCh38) have been identified in humans so far [13]. Gene expression is controlled by either mRNA target modification or by inhibition of translation [14]. According to Condorelli et al. [15] and Kataoka et al. [16] microRNA are also involved in cardiac regeneration, remodeling and hypertrophy along with their involvement in cardiac development.

3. Single nucleotide polymorphisms in microRNA

With the advance of human genome project, naturally occurring variations in human DNA, such as, polymorphisms have become an important part of genomic analysis. Out of the total polymorphisms of the DNA, 90% are SNPs [17]. SNPs occur in genomic DNA at every 1000–2000 bases in a human chromosome [18]. On an average, one SNP is available at every 1.9 kb, out of these, 60,000 SNPs fall within coding and untranslated region of exon. 85% of these axons are found within 5 kb of nearest SNP [19]. In light of these events, it is safe to say that SNPs can be an excellent tool for haplotype analysis and high throughput genotyping, due to its binary nature. Also, SNPs show a low rate of recurrent mutations hence they can give us a stable picture of human genome history [20].

The most common type of polymorphism found in microRNA is single nucleotide polymorphisms. SNPs among miRNA may potentially affect them at different stages, including, maturation of miRNA, the gene silencing machinery, the structure and expression of the mature miRNA. In addition, these single nucleotide changes can also affect base pairing at the target site, it may affect miRNA regulated gene expression therefore, potentially increasing disease risk, such as, cancer [21,22]. Sun et al. studied the effects of SNPs on generation and function of mature miRNAs. They reported that naturally occurring SNPs can impede or enhance processing of miRNA and also alter the sites of processing [23]. As miRNAs are small functional units, single nucleotide changes in the precursor and the mature miRNA sequence can cause the genesis of a new microRNA by changing its biological function. In a study conducted by Pauley et al., X-linked miRNAs were examined, which indicated that the mutant alleles could be determinants in the disease etiology [24]. In SNPs one nucleotide is replaced by another, sometimes resulting in a mismatch sequence, for e.g., miR-146a polymorphism (rs2910164) causes a change from G-U pairing to a C-U mismatch in the stem structure of the pre-miRNA [25]. miRNA single nucleotide polymorphisms, their positions and their sites of polymorphism have been summarized in Table 1.

4. Role of miRNA SNP in CVD

Evidence collected through various association studies indicate that SNPs of miRNA play an important role in CVD development and its progression. These studies have been carried out in different populations belonging to different geographical areas and different genetic makeup. However, work still needs to be done to fully understand the extent of relationship between these miRNA polymorphisms and disease.

4.1. Coronary artery disease

Studies conducted in last decade have greatly increased our understanding of association between miRNA SNPs and CAD. Epidemiological studies [26,27] conducted in the past have accounted genetic factors to be CAD risk in 40–60% of population, however, out of those 40–60%, 10% of CAD cases are due to heredity [28]. The heritability of Myocardial Infarction (MI) is 60% [29], genetic variability of atherosclerosis is estimated to be 50% [30]. Therefore, other factors such as environmental factors, miRNA polymorphisms etc. may also play a role in prevalence and pathogenesis of CAD. Association studies analyzing the relationship of miRSNPs and cancer have been carried out in great depth and numbers, but effects of SNPs of miRNA on CAD has not been studied very well.

4.1.1. miR-146a (rs2910164)

According to a case control study carried out by Xiong et al. [31] in Chinese Han population, individuals carrying C allele have increased susceptibility to CAD. Additionally, this allele also confers higher expression level of mature miR-146a. The change from G to C allele in precursor miRNA tends to cause increased expression of mature miR-146a in peripheral blood mononuclear cells (PBMCs) of CAD patients