**Identification Of Genetic Risk Factors Associated With Myocardial Infarction**

1. **Introduction**

Myocardial infarction (MI) is a complex multi-factorial, polygenic cardiovascular disease (CVD) arising from an interaction between genetic makeup of individuals and various environmental factors. Developing countries now experience a much greater burden of MI than developed countries do, and the projections are also suggesting exponential increase of this burden in the future. The absolute reasons for MI are context dependent and differ with different geographical settings. In addition, plethora of other factors such as food habits, lifestyle, high blood pressure, cholesterol, obesity, smoking, diabetes, and physical inactivity adds to the MI burden1,4,5. Other independent variables are equally responsible for MIs. For instance, social economic status, poor hygiene, cultures, and lifestyle plays a larger role 1,2,3,4,6,7. With respect to India, where globalization is happening at a larger scale, life styles of individuals are changing tremendously in recent years that contribute towards increased MI susceptibility.

The discovery of millions of DNA sequence variants in the human genome has created the possibilities of studying the genetic basis of CVDs and other diseases in different ethnicities. In recent years, genome wide association studies (GWASs) are proven to be promising in identifying rare and common variants associated with many diseases, where the whole genome is mapped and gene loci affecting susceptibility or resistance were identified subsequently. The whole genome mapping has revealed a large number of genetic loci involved in susceptibility to many infectious diseases. Over the last four decades, attempts to define the genetics of CVD have been restricted to that of rare single gene disorders, primarily involving cholesterol. The candidate gene study approach has been successfully used to discover the susceptibility loci for several major diseases8-12. Many candidate gene approaches also have shown association with CVDs. The most striking observation of that era was by Brown and Goldstein describing a mutation in the low-density lipoprotein receptor responsible for familial hypercholesterolemia17. The cutting edge technology GWAS was the most successful approach to identify the variants and genes 13,14. Only in the last decade has it been possible to pursue genetic predisposition underlying complex multi-gene disorders, such as coronary artery disease (CAD). This was heralded by the development of high-density microarrays containing hundreds of thousands of single nucleotide polymorphisms (SNPs) as DNA markers and the requisite platforms to perform unbiased GWAS18. A decade later, hundreds of loci associated with many CVDs and traits have been identified. This genetic bounty is the yield of GWAS, which involve testing of a large set of genetic variants in case and control subjects from a population to determine which variants are associated with the disease in question. Further, the role of genetic variants and risk factors in the management of MI is yet to be determined in Indian population.

1. **Importance of proposed research/investigation**

The present study might give a basis to answer how inter-individual variability can possibly influence a MI outcome in a given ethnic population of India. We will apply the combined approach that discovers the common and rare SNPsinvolved in enhancing the MI risk and testing critical aspects of the alternative models with highly targeted data with up-to-date analytical techniques from the latest genomic data.

The limited access to high through put techniques such as GWAS in developing nations somewhat also hinders the improvement of the disease prevention tools. On the other hand they are expensive. But this is not solely due to the reasons mentioned above, but also with the exclusive addition of the complex population structure of India, which has played a major role in spread of disease susceptible genes in the subcontinent. Keeping in mind its important geographical position, high effective population size, high level of endogamy and long term load of various diseases. Such unique feature might have given rise a high number of common as well as local variations. Thus, a chance of losing true susceptible variant is very likely in case of a variant which is not ‘identity by descent’ in different continental drifts. We will explore the convergent vs divergent evolution of MI susceptible as well as resistant genes among South Indian populations. Applying the genome-wide approach in South India will certainly be revolutionary to increase the power to detect the novel susceptible loci. Moreover, the use of whole genome analyses will add finest level of scrutiny. And none of the study so far tackled on the India especially south India core populations to understand the core mechanism. Therefore, on the background of our deep population genetic expertise, we have taken this study with high-resolution analysis with cutting edge genomic technology, to reveal the robust association between genetic markers and susceptibility of CAD disease.

With the extreme utilisation of GWAS and candidate gene approach results we are confident that we will be able to identify most of the common and rare variants of MIs in Indian population.

1. **Objective**

* To do GWAS in a subset of MI case and control samples using Illumina microarray platform
* To identify common and rare variants responsible for MI
* To identify variation in selected genes, which may be responsible for susceptibility to develop MI
* Validation of MI’s associated variants in a case-control cohort

1. **Methodology**

The peripheral blood will be drawn from controls who are not diagnosed as MI and subjects who are diagnosed with MI from cardiac departments of local hospitals in Mangalore. The blood sample collected from both subjects and controls will be subjected to DNA isolation using salting out method followed by phenol-chloroform purification and quantified by nanodrop. Few candidate single nucleotide polymorphisms (SNPs) will be studied in both case and control sample groups. A subset of samples will be subjected to study GWAS using bead array chips commercially available from Illumina microarray platform. The high-throughput SNP genotyping array data will be analyzed to identify common and rare variants that are associated with MI. These identified variants will be validated on larger case-control cohorts.

1. **References**
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