Almost 60% of the Human population is thought to have a genetically-influenced disease representing a major impact on the economy and health services all over the world. Identification of genes implicated in genetic and genetically influenced diseases facilitates early prediction of risk, diagnosis and provides hope for the development of drug- or gene-based therapies.

One goal of genetic research is to better understand the mechanisms of the disease so that new treatment approaches and preventative measures can be proposed. Because researchers now understand that the genetic contribution to many diseases is complex and that the same disease does not manifest in the same way in all people. Descriptions that involve gradients of sickness and health are typically more effective than those that classify individuals as either "sick" or "healthy."

Obesity can be seen as the first wave of a defined cluster of noncommunicable diseases called "New World Syndrome," creating an enormous socioeconomic and public health burden in poorer countries. The World Health Organization has described obesity as one of today’s most neglected public health problems, affecting every region of the globe (Pendekar, 2008).

Obesity has always existed in human populations, but until very recently was comparatively rare. The availability of abundant, high fat and processed foods in the last few decades has, however, resulted in a sharp rise in the prevalence of obesity in westernized countries. Although it is the obesogenic environment that has resulted in this major healthcare problem, it is acting by revealing a sub-population with a pre-existing genetic predisposition to excess adiposity. There is substantial evidence for
the heritability of obesity, and research in both rare and common forms of obesity has identified genes with significant roles in its etiology. Application of this understanding to patient care has been lagging. Until very recently, the health risks of obesity were thought to be well understood, with a straightforward correlation between increasing obesity and increasing risk of health problems. It is becoming clear, however, that the location of fat deposition, variation in the secretion of adipokines and other factors govern whether a particular obese person develops such complications. Prediction of the health risks of obesity for individual patients is not straightforward, but continuing advances in understanding of genetic factors influencing obesity risk and improved diagnostic technologies mean that the future for such prediction is looking increasingly bright.

Obesity accounts as one of the leading causes of preventable death. Complications of obesity include cardiovascular risks, hypertension, dyslipidemia, endothelial dysfunction, type 2 diabetes mellitus, impaired glucose tolerance, acanthosis nigricans, hepatic steatosis, premature puberty, hypogonadism and polycystic ovary syndrome, obstructive sleep disorder, orthopedic complications, cholelithiasis and pseudotumor cerebri. Genetic, molecular and environmental factors play an important role in the assessment and management of obesity.

Obesity has reached epidemic proportions globally, with more than 1 billion adults overweight and at least 475 million of them clinically obese. When Asian-specific cut-off points for the definition of obesity (body mass index >28 kg/m²) are taken into account, the number of adults considered obese globally is over 600 million- and is a major contributor to the global burden of chronic disease and disability.
Often coexisting in developing countries with under-nutrition, obesity is a complex condition, with serious social and psychological dimensions, affecting virtually all ages and socioeconomic groups. Increased consumption of more energy-dense, nutrient poor foods with high levels of sugar and saturated fats, combined with reduced physical activity, have led to obesity rates that have risen three-fold or more since 1980 in some areas of North America, the United Kingdom, Eastern Europe, the Middle East, the Pacific Islands, Australasia and China. The obesity epidemic is not restricted to industrialized societies; this increase is often faster in developing countries than in the developed world.

Negative effects of obesity on male fertility have been described as early as the 10th century by Avicenna, a Persian scientist and medical doctor in his encyclopedic medical book “The Canon of Medicine”. However, until recently, the possible relationship between obesity and male reproduction has been largely ignored. This is surprising, as the male gamete contributes to half of the genetic material of the embryo and now more that 50% of the reproductive age males are overweight (Begg et al., 2008). Male infertility accounts for 40-50% of infertility (Hirsh, 2003). It is commonly due to deficiencies in the semen, and semen quality is used as a surrogate measure of male fecundity (Cooper et al., 2009). In men, hormone disorders, illness, reproductive organs trauma, obstruction, and sexual dysfunction can temporarily or permanently affect sperm and prevent conception. Some disorders become more difficult to treat as long as they persist without treatment.

In India about 15–20% of married couples known to be sub- or infertile category (Seshagiri, 2001), opt for medically assisted reproductive technology (MART).
However, a substantial portion of infertile patients still remain without help for various reasons such as lack of adequate treatment options and their accessibility, high cost and fear of conceiving and bearing potentially abnormal offspring. This is despite the fact that over the years MART has become useful for couples with infertility, with a good success rate of about 20–30% globally. There is a need for a multidisciplinary comprehensive infertility care, which should also involve structured management strategies, and this should include clinical evaluation, prenatal genetic diagnosis (PGD), genetic counselling, patient education, informed consent and most appropriate and cost effective MART approaches to infertility treatment (Liebaers et al., 1998; Fasouliotis and Schenker, 1999). The extremely limited health care resources available in the country make this particularly important. Preliminary studies in the mouse models suggest that a frameshift mutation in JHDM2A gene affects male mouse fertility and can induce male obesity as well. Our current study aimed to determine whether different single nucleotide polymorphisms within three exonic regions of the human JHDM2A gene will be found between obese and non-obese infertile male population compare to controls as it was hypothesized that sequence variation in form of SNPs within the exons 20 to 25 of JHDM2A gene differ between cases and controls and play a role in the onset of obesity and infertility in male mouse. The ultimate goal of this study is to determine whether our candidate gene (JHDM2A) appears to play a role in the pathogenesis of obesity induced infertility in men.

Thus, in the present investigation an attempt has been made to understand the genetics of male infertility and effect of obesity on male fertility potentials or coincidence of obesity and infertility due to genetic variation in Mysore, South India. The findings and implications of this study are compiled in the following sections:
**Section I:** Review of literature about male obesity and infertility

**Section II:** The pathophysiology and genetic factors involved in obesity and male infertility. The physiological impact of obesity on fertility potential in men and overall genetic analysis of candidate gene in Mysore population

a) Clinical manifestation based on anthropometric and semen analysis

b) Analysis of seminal Reactive Oxygen Species level

c) Analysis of proinflammatory pathway by measuring the seminal level of Interleukine-6

d) Analysis of sperm Protamine-1 level

e) Analysis of exon 23, 24 and 25 of the *JHDM2A* gene for sequence variation

**Section III:** Summary and future prospects of these investigations.

**Section IV:** The literature cited in this thesis

**Section V:** The list of publications from this work.