Life expectancy has increased over the years and hence the population of older people. Older people are more vulnerable to age related disorders, disabilities and dementia (http://www.who.int/mediacentre/factsheets/fs381/en/). With the rapidly aging world population the number of people suffering from dementia is expected to reach 65 million by the year 2030. Dementia is the decline in mental ability and cognitive functions like, thinking, memory, reasoning and daily life activities. Among older adults Alzheimer disease (AD) is known to be the most common cause of dementia. Other types of dementias include vascular dementia, dementia with Lewy bodies and a group of diseases that contribute to fronto-temporal dementia. AD is third leading cause of death among older adults in U.S.A and overall ranks as sixth leading cause of death (Association, 2016). It is named after Dr. Alois Alzheimer who first reported the disease in 1906 as *"*A peculiar severe disease process of the cerebral cortex" and observed distinctive plaques and neurofibrillary tangles in the brain histology (Hippius and Neundorfer, 2003).

Even after 110 years of the discovery of the disease exact causes of AD are not understood and there is no cure. According to World Alzheimer Report 2015, 44 million people are living with dementia worldwide (Prince, 2015). It is expected to mark 131.5 million by 2050. According to World Health Organization (WHO), treating and caring for people with dementia cost the world more than US$ 604 billion per year (Prince et al., 2013). This includes the cost of providing health and social care as well the reduction or loss of income of people with dementia and their caregivers.

There are almost 900 million people aged 60 years and over living worldwide. Rising life expectancy is contributing to rapid increases in this number, and is associated with increased prevalence of chronic diseases like dementia. According to United Nations data the total population of the Asia pacific region in 2005 was estimated to be 3.58 billion. The population over 65 years was estimated as 238.9 million with 37.2 million people aged over 80 years. The number of new cases of dementia in the Asia-pacific region is projected to increase from 4.3 million new cases per year in 2005 to 19.7 million new cases by 2050 (Economics, 2006). The reported incidence rate for AD has been lower in Asian countries than in the industrialized world (Chandra et al., 2001, Chen et al., 2011, Liu et al., 1998, Yoshitake et al., 1995, Zhang et al., 1998).

The 15 Asia Pacific member organisations of Alzheimer Disease International (ADI) are located in Australia, China, TADA Chinese Taipei**,** Hong Kong SAR, India, Indonesia, Japan, Malaysia, New Zealand, Pakistan, Philippines, Singapore, South Korea, Sri Lanka and Thailand**.** Other countries included in this analysis are Bangladesh, Bhutan, Brunei Darussalam, Cambodia, Macao, the Democratic People's Republic of Korea, East Timor (Timor Leste), Laos, Myanmar, Nepal, Papua New Guinea and Vietnam. The total population of the region in 2005 is estimated from United Nations data as 3.58 billion (Fig. 1.1). The population over 65 years is estimated as 238.9 million with 37.2 million people aged over 80 years. Report states that number of people with dementia in Asia pacific region will increase from 13.7 million people in 2005 to 64.6 million by 2050 (Economics, 2006).

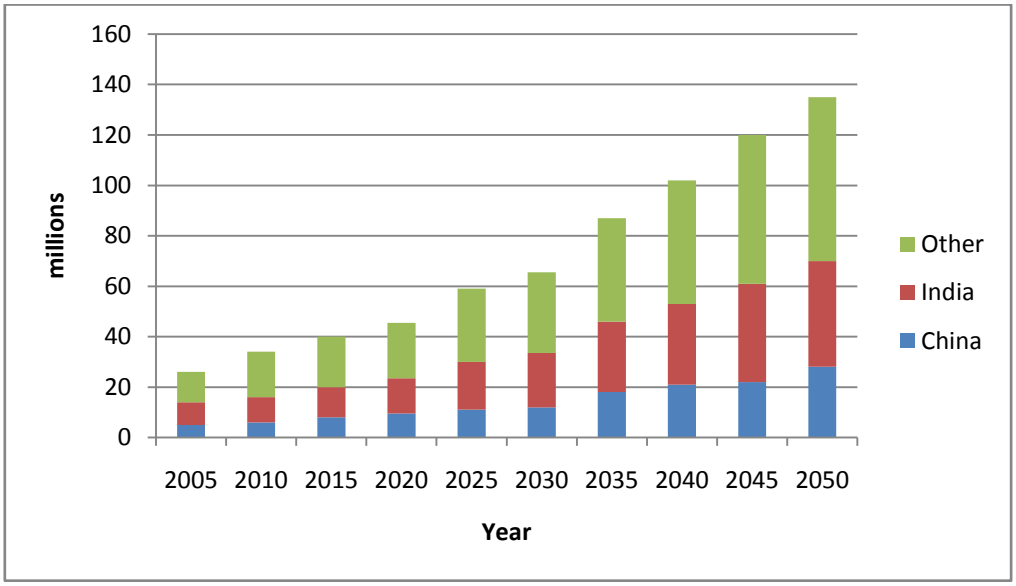

Fig. 1.1 Total prevalence of dementia in China, India and other region from year 2005-2050

According to Dementia India Report 2010 an estimated 3.7 million Indian people, aged over 60, were suffering from dementia (2.1 million women and 1.5 million men). The prevalence of dementia was observed to be increased steadily with age and higher prevalence was marked among older women than men (Fig. 1.2). India has a rapidly growing aging population which exceeds 100 million. Studies on dementia prevalence have not been consistent across the country. Prevalence studies in Asia have been done but statistics are not accurate in Asia.

Public awareness about dementia in India is low and is considered as normal part of ageing. There is no special emphasis on dementia diagnosis and management of disease also for providing training to healthcare professional. No structured training is provided to healthcare people for recognising and managing the disease. Majority of people take dementia as a normal ageing issue and not as any health problem. Though with the changing times and increased number of reported dementia cases people are becoming more aware. The carers are not provided any assistance from health services or agencies. Most importantly there is no government body/department taking care of this aspect of mental health for ageing people and no policy for dementia services in the country (Sinha, 2011). Low awareness has resulted in silent suffering of the patient and carers.

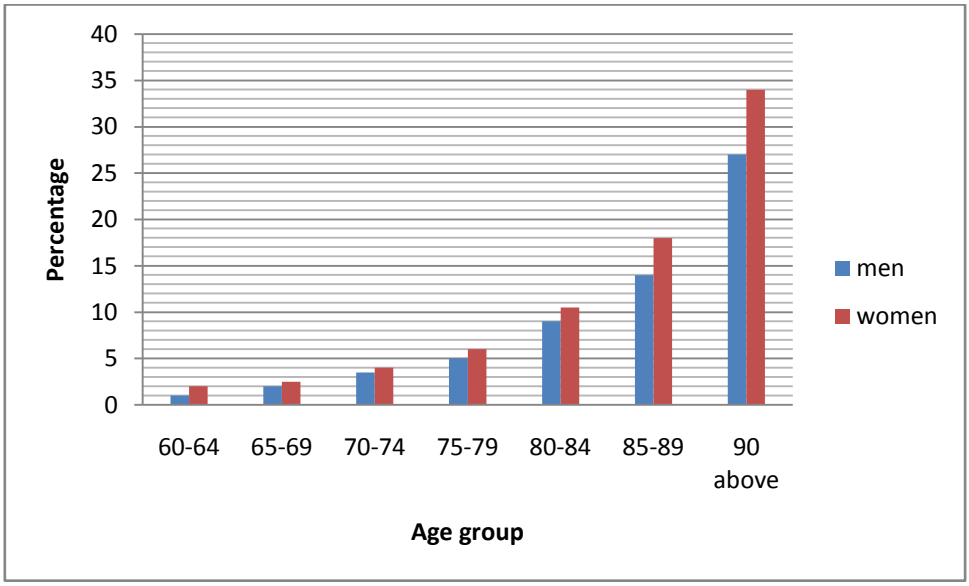

Fig.1.2 Prevalence of Dementia in India by 2010

Their exists an urgent demand of trained health care professionals to take care of older sections of society to meet the pace of demographically ageing population (Grady, 2011). Also health professionals should be trained to identify conditions like dementia which is the major health problem occurring in old age (Oliver et al., 2014). Effective strategies and decisive action is required to meet this challenge. Epidemiological research which identifies modifiable risk factors and preventive interventions in order to reduce the incidence of the disease is required for the improved understanding of the disease and devising better therapeutics.

Worldwide dementia, specifically AD has been recognised as a global cause hence needs to be devising its cure earliest. Percentage change in age adjusted death rates for selected cause of death in U.S.A. 2000-2008 (Fig.1.3) clearly indicates the importance of Alzheimer (http://www.usagainstalzheimers.org/crisis).

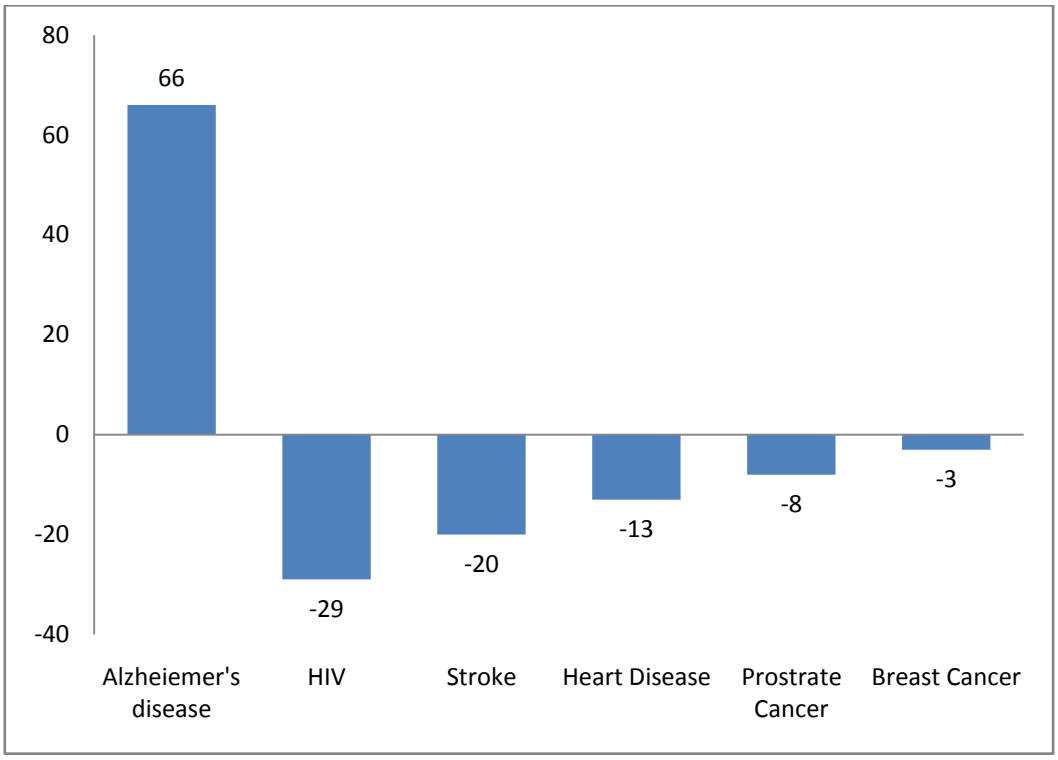

Fig. 1.3 Change in number of deaths, 2000-2008

An action plan for dementia based on the minimum actions required for the care of people with dementia was presented at the 20th International Conference of Alzheimer's Disease International in 2004 in Japan-the Kyoto Declaration (Declaration, 2004). The Sigma Kappa Foundation presented the Alzheimer's Association with the $1 million lead gift for the Women's Alzheimer's Research Initiative at Sigma Kappa's 87th National Convention held in Chicago. It will fund innovative research focused on women including studies to understand why more women are living with this disease and studies led by female researchers working to advance Alzheimer's and dementia science.

The first-ever Alzheimer's Association Sex and Gender in Alzheimer's (SAGA) research grant awards will provide $2.2 million to nine projects to advance understanding of the

disproportionate effect of Alzheimer's disease on women (http://www.alz.org/media_current_news_releases.asp). The proposed 2016 federal budget allocates an additional $350 million for Alzheimer's research, a 60 percent boost that will bring total funding to $936 million (Association, 2016).

Alzheimer is a progressive, irreversible disorder affecting cognitive function and is characterized by gradual loss of cognitive functions including behavior, memory, recognition, and thinking. In common man terms it is said to be the dementia or disease of old age. It is true that majority of people affected by alzheimer's are above 65 hence the greatest risk factor for AD is age but it is not just the disease of old age. The early onset form of AD might be attributed to inherited genetic mutations. 5-10 % of Alzheimer cases are of early onset of disease i.e. individuals of the age of 40-50 years (Zhu et al., 2015).

AD is a neurodegenerative disorder which has very complex aetiology and has no cure. It is associated with gradual loss of memory and other functions. The two most starking pathological feature of the disease include presence of senile plaques deposits and neurofibrillary tangles (NFTs). Senile plaques are the accumulation of amyloid beta (Aβ) peptide in extracellular spaces whereas NFTs is the aggregation consisting of microtubule associated tau protein in phosphorylated state inside the neurons. Eventually it leads to loss of function followed by neuronal death. It has been demonstrated that the spreading of NFTs across the brain exhibits high correlation with the cognitive impairment status in AD (Nelson et al., 2012).

Advancing age is one of the most important of these but people less than the age of 65 years is also found to be affected by this disease. Other risk factors include family history, presence of ApolipoproteinE 4 (APOE-e4), mild cognitive impairment, sex, obesity, diabetes, high blood pressure, lifestyle and head trauma. Till date many studies has been done stating genes and factors responsible for disease progression (Hickman and El Khoury, 2014). Genes up regulated or down regulated, pathways altered in the disease are studied to a large extent (Miller et al., 2013). Apolipoprotein E (Apo-E) gene has direct role in Aβ clearance and is known as the main risk factor for AD (Liu et al., 2013). Apo-E is involved in lipid transport from one cell or tissue type to another and hence regulates lipid homeostasis. It is a principal cholesterol carrier in the brain (Mahley et al., 2000).

Rare variants in the amyloid precursor protein, presenilin 1, or presenilin 2 genes were known to be the first associated ones with the AD (Hutton, 1997, LaFerla et al., 2007).

PCDH11X gene was stated as an important susceptibility locus for development of late-onset Alzheimer's disease (Carrasquillo et al., 2009), which was later shunned by further studies of Lescai *et al.,* (Lescai et al., 2010, Miar et al., 2011). On the basis of systems biology approach using WGCNA (Weighted Gene Co expression Network Approach) Miller *et al.,* confers *ABCA1, MT1H, PDK4, RHOBTB3* as susceptible loci for the disease (Miller et al., 2013).

Genome-wide association studies (GWAS) have listed large number of putative genes for AD and the associated genetic risk factors (Van Cauwenberghe et al., 2015). These genes need to be studied for their pathophysiological role in AD in order to develop therapeutics for this disease (Shen and Jia, 2016). Hence polygenic nature of this retrogressive disorder can be stated by the hypothesis that mutation in multiple genes is the root to disease manifestation, which makes this disease highly complicated to understand and to find an explanation for devising combat measures. Thereby AD has been christened as a multifactorial disease which implicates its association with varied genes, pathways, functions and diseases.

There exists no study which provides overall picture of the disease considering majority of the responsible factors. Several studies have been carried out to elucidate other related genes but Alzheimer's aetiology still remains unexplained. According to a study at NewYork city higher dementia risk in individuals aged 65 to 76 years was associated to elevated waist circumference (Luchsinger et al., 2007). Risk of developing AD is rising incredibly with the increasing obese population all over the world as obesity and diabetes are two of the contributors to AD (Harris et al., 1998, Mann, 2000). Histological examination reveals higher levels of Aβ , Tau (τ) and Amyloid precursor protein (APP) deposits in the brain samples of obese (Body mass index, BMI > 45) patients of age above 65 years which was comparable to people with established AD (Mrak, 2008). Which pathological mechanisms are responsible for the disease progression is not known clearly and how obesity leads to manifestation of AD needs to be explored more.

A study states that insulin plays a significant role in modulation of learning memory and synaptic plasticity (Watson and Craft, 2004). In the brain it competes with Aβ for insulin

degrading enzyme (IDE) and have been found to have role in amyloid clearance (Farris et al., 2003). Studies state that deterioration of cognitive and motor function is accelerated by increasing total body fat. According to Framingham heart study the marked impairment of cognitive function in patients with obese compared with non-obese counterparts have also been reported (Elias et al., 2003).

In AD cases without an ApoE4 allele, dysfunction associated with diabetes and obesity were enriched (Profenno and Faraone, 2008). All these studies highlight an inverse correlation between higher body weight and memory function in adult human subjects. Sex and gender another risk factor has further gained support for developing AD by recent evidence suggesting that brain's so called cognitive reserve is reduced in women (Laws et al., 2016).

Alzheimer association have found that almost two-thirds of American seniors living with AD are women i.e. more women suffer with AD than men (Association, 2016). In human brain across the lifespan of male and females, aged 20-99 years, sexually dimorphic gene expression changes has been found (Berchtold et al., 2008). Meta-analysis of 13 population studies from across United States, Europe, and Asia (Gao et al., 1998) has indicated that women are at significantly greater risk of developing AD supporting the sex-biasness of the disease. Sex has been implicated in AD pathology as women being more affected by AD (Carter et al., 2012).

In AD etiology estrogen have been found to play an important role as it has been found to have neuroprotective role (Musicco, 2009). Estrogen deficiency-induced memory dysfunction and risk of Alzheimer's disease has been reduced by the estrogen replacement therapy in humans (Brinton, 2001). There are numerous studies implicating role of mitochondrial dysfunction in AD etiology. Since in AD, brain is observed to be under oxidative stress there is increase in production of reactive oxygen species (ROS) (Mosconi et al., 2010) which is an outcome of altered energy metabolism (Duara et al., 1993). Hence maternal inheritance of AD is speculated as mitochondria are maternally inherited. Although disrupted mitochondrial function might not be associated with maternal inheritance. Also reduced COX (cytochrome c oxidase) activity has been observed in AD brain implicating potential role of mitochondria in AD (Parker and Parks, 1995). It has been reported that cells lacking mitochondria are protected against Aβ toxicity directly implicating role of mitochondria in AD pathology (Cardoso et al., 2001).

Exactly how and which genes play their role in disease progression are so far ambiguous. The causes of disease etiology and progression are unknown and yet to be discovered. There is a dire need to find out and target genes responsible or disease progression. With no cure on horizon and increasing global aging population AD stands as an unsolved mystery on the face of mankind. The fact that there is no assured cure or vaccine of the disease despite of so much development and advancement in our technology states the lacuna in understanding of Alzheimer's.

This diagnostic dilemma even after 100 years of first discovery of AD poses a grave challenge to the scientific community all across the globe (Hippius et al., 2003). Detailed knowledge about various risk factors responsible for AD and identification of those factors which would help in reducing the risk of dementia is urgently required to control this silent epidemic. There exists a need to develop better research capacity in order to have better therapeutics. Keeping all this in focus this study aims to show some light on the unknown path of Alzheimer manifestation in order to have better understanding of disease aetiology.

Many studies have been done in future but neither of them has considered all AD associated genes together in order to understand the disease better. The *in silico* analysis or a combinatorial study of all these genes together might be helpful in focusing on unexplored areas of AD. Since genes behave differently in different environment and in influence of other genes it is highly intriguing to explore the effect of all genes together in a sample. Present study is an effort to highlight disease associated genes in order to have an improved understanding of the disease and develop effective therapeutics.

This study is a synergistic work of sporadic studies happened so far in order to have better understanding of the disease and highlight many lesser studied and unexplored gene targets for vaccine and drug design. Many studies have been done exploring factors and genes responsible for AD and obesity separately. None of the studies relates the gene expression related to obesity and AD together. Molecular mechanisms involved in relation to these diseases are not studied earlier. The study of obesity genes expression in whole transcriptome of AD and control brain samples might be helpful in order to understand the unexplored relation between AD and obesity better.

In order to understand AD etiology and pathogenesis broad interplay of various factors, genetic, hormonal and environmental, need to be understood. The role of sex and gender differences in the onset and course of AD remains ill-defined and demands further attention. Despite recent advances in the understanding of clinical aspects of sex differences in AD, the underlying mechanisms, for instance, how sex modifies AD risk and why the female brain is more susceptible to AD, are not clear. The area of gender differences in AD and in neurodegenerative processes appears to offer great promise for the future development of better strategies of intervention for patients.

The current study aims to explore novel and unexplored gene targets associated with human sex chromosomes, mitochondria and genes known to be sex biased in order to answer the hypothesis that AD affects men and women differently. Further the expression of sex chromosome associated, mitochondria and sex biased genes in AD samples from different region of brain can be studied. Discovery of obesity genes which were also involved in AD may be helpful in understanding and identifying novel therapeutic targets for AD. AD has become a global threat with the increasing number of people affected with every passing minute. High prevalence of the disease with no cure on horizon is a biggest challenge to the scientific fraternity all across the globe. How sex, obesity, gender affects the AD etiology and responsible for disease manifestation are quite intriguing and challenging. Keeping these caveats in AD research in picture following objectives has been framed for the study.

1.1 Objectives of the Research:

1. Collection of all Alzheimer's associated genes from literature and databases and their clustering according to function and similarity.
2. Comparative transcriptome (RNA -Seq) analysis of AD and normal brain.
3. Differential expression and association studies of AD, obesity and sex associated genes on transcriptome dataset.