ABSTRACT

Alzheimer disease (AD) is a progressive, neurodegenerative disorder with no cure. Even after 110 years of discovery of the disease poorly understood AD etiology poses a grave challenge to researchers. Numerous sporadic studies have been carried out but a holistic work considering all genes associated with AD have not been carried out. There exists a dire need of a combinatorial study comprising Alzheimer associated genes (ADA) for enhanced understanding of AD. Various factors have been associated with AD like obesity and sex. Etiology of AD is different in male and female and female brain is more susceptible to AD but underlying molecular mechanism is unknown. This gender biasness of disease is well-known but unexplained. Functional and sequence based clustering of ADA genes revealed that they have diversified function supporting multifactorial nature of AD. Further expression analysis of AD transcriptome was correlated to ADA and their clustering output. Explicitly, Gonadotropin releasing hormone receptor pathway was found to be most significantly associated with AD. Significant no. of obesity genes was found to be common in AD majority of which on pathway analysis clustered into signalling pathways. Sex–associated genes (X, Y, Mitochondria encoded and sex-biased genes) along with ADA and obesity genes were studied on AD transcriptome for their expression. Significant no. genes from all the three classes were found to be differentially expressed (DE) which indicates their association with AD. Almost all DE genes were in correlation with their molecular function based enrichment analysis and can be further explored for their therapeutic potential. For e.g. *MT-T1* gene, up-regulated in all AD samples, can be considered as potential drug target since reduction in oxidative stress may have therapeutic effect in AD. Significant no. of non-protein coding genes was also found to be DE in AD. This is the first study focussing Y chromosome transcriptome in context to the AD disease. Majority of the genes were down-regulated thereby conforming lower transcriptional activity in Alzheimer brain. Repressed activity of Y chromosome genes in AD samples justify it's importance and probably explains susceptibility of females in AD. Some Tc factor encoding genes and their target genes were found to have significant role in AD. These results justify current approach and warrants to explore the role of all DGE genes in AD through further experimentation. It is an attempt to explore the association of AD with obesity, sex and gender in order to have broad understanding of AD and has proposed different therapeutic targets and pathways.

Keywords: Alzheimer, gene, transcriptome, obesity, sex