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Prediction of novel drug target Involved in psychosis in Alzheimer Disease: A Computational Network study

Mrinal Mirsra[1]

Kiruba Thangam. R[2]

Febin Prabhu Dass. J[1*]

[1] Bioinformatics Division, School of Biosciences and Technology, VIT University, Vellore. Tamil Nadu State, India. 632014.
[2] Enterprise and Cloud Computing, School of Information Technology & Engineering, VIT University, Vellore. Tamil Nadu State, India. 632014.

Corresponding Authors:
Febin Prabhu Dass. J
Associate Professor,
Bioinformatics Division,
School of Biosciences and Technology, VIT University,
Vellore, Tamil Nadu, India. 632014.
Email: mail2febin@gmail.com

Abstract:
Alzheimer (AD) disease is the most frequent form of dementia. Several structural and functional genomic factors are strongly associated with AD candidate genes, including age of onset, cognitive decline and amyloid depositions. Serotonin (5-TH) receptors play an important role in psychosis in AD with cognitive impairment. This study is based on insilco identification and prioritization of the differentially expressed genes of the genetic network involved in AD. Fourteen 5-HT candidate genes interaction network associated with AD was generated using agilent literature search cytoscape plugin. The organic layout shows cross-interaction between the genes set. On merging the genetic network with gene expression profile data, notable changes in interaction patterns were observed. These changes revealed 5-HTR2A, 5-HTR2C and 5-HTR4 as important genes in AD. Further refinement with Enrichment Map indicated 5-HTR2C as novel candidate gene that showed high functional significance in correlation to Alzheimer's disease. Our result will be a crucial factor for better understanding of the genetic pathways involved in causing psychosis in AD and will form a future landmark in developing target based drug therapies against this disease.

Keywords: Within family interaction;co-expression;major target, computational network analysis of alzheimers

Introduction:

Alzheimer disease (AD) is a neurodegenerative disorder propagating dementia .This is clinically characterized by progressive cognitive impairment associated with severe neuropsychiatric disturbances. Deregulation of serotonergic neurotransmitter system is credited to cause AD on wide scale. The impaired neuronal signalling cascades serotonergic deregulation affecting the proteolysis of the amyloid precursor protein (APP) and stimulate amyloid formation in the brain.

Although the origin of psychotic symptoms in Alzheimer's disease (AD) is multi-factorial, alterations in serotonergic neurotransmission are often implicated. Polymorphisms of the serotonin receptor (5HT) are associated with hallucinatory symptoms and delusions in demented and non-demented cohorts. 7 major receptors classes (5-HT1-7) mediates 5-HT metabolic pathway comprising a total of 14 distinct mammalian 5-HT receptor subtypes. Recent genetic studies in AD showed co-existence of several polymorphisms of the serotonin neurotransmitter genes and neuropsychotic symptoms. Gene polymorphism in 5-HT receptor resulting in the change of the gene expression level has been reported to be associated with visual and auditory hallucinations or psychosis in patients with AD. A 44–base pair (bp) insertion (the long or l form) of the 5-HTT promoter region (5-HTTPR) was reported to be associated with psychosis and aggression in AD. A variable number tandem repeat (VNTR)

polymorphism in intron 2 of the 5-HTT gene was also reported to associated with susceptibility to unipolar or bipolar depression in AD. The change in the specific genetic expression pattern also results in cascading the change in expression pattern to the other associated genes of the genetic network pathway directly or indirectly. This change can vary the resulting gene products of diverse genes in the network greatly affecting the other different pathways.

In our study, Multiple 5-hydroxytryptamine (5-HT) genes along with other genes of the genetic network were observed but only few of these 5-HT genes when differentially expressed are reported to cause Alzheimer disease (Fig 1). We used Cytoscape [4] for generating and visualising genetic interaction network. Different Cytoscape plugins were used to assist the generation and analysis of the network with extreme accuracy. Obtained Genetic network comprising the candidate genes were then prioritize and analyzed by merging with the genetic expression of the differentially expressed genes in AD which on further analysis with enrichment map generated on the basis of differentially expressed genes regrouping and categorising the genes corresponding to their expression giving the most refined results.

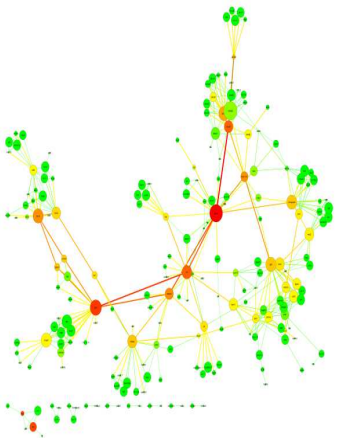

Fig 1: Network before merging genetic map

Materials and Methods:

Dataset Collection

Serotoninergic receptors previously reported to play important role in Brain ageing and based on extensive literature searching, we selected 14 candidate genes which code these serotoninergic receptors. Collections of expression profiles for the 98 important genes involved in the genetic network were done from NCBI Geo profile database.

Development of genetic network using Cytoscape

Cytoscape is used for directing and apprehending networks using Zoomable User Interface. The directing through this interface is based on two processes namely zooming and panning. Zooming changes the dimensions of the view based on the user need. Panning enables the users to direct the focus of a screen to different location of a view. Agilent Literature search [5] was used to scan the genetic network through published literatures. It work parallely within cytoscape and is a meta search tool that have a ability of integrating the information and knowledge extraction to generate the genetic network from literatures using Pubmed, OMIM and USPTO search engines when fed with the candidate genes. For generating the genetic network it uses User context-based symbol normalization. Genetic expression profile data of all the genes of the genetic network from NCBI geoprofile database were extracted and saved as a file in pvals format. The file was merged with normal genetic network. Enrichment map[7] (Fig 2) for the differentially expressed genes were generated for further analysis and refinement of the result which clusters the genes according to correlation with each other giving three clusters of gene differentiated on the basis of the preference

of expression profile data of the differentially expressed genes.

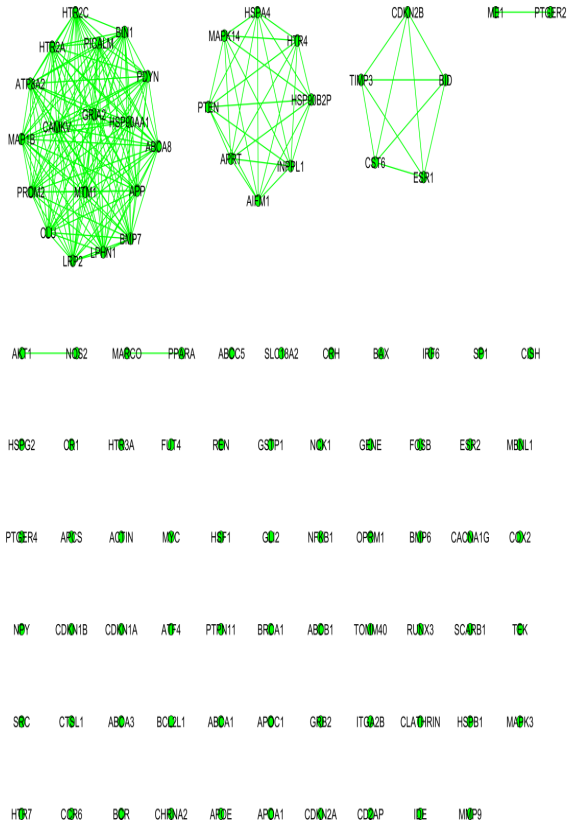

Fig 2: Enrichment Map for the expressed genes

Visualisation of the genetic network

Vizmapper [6] was used for assisting the Visualisation of the genetic network merged with genetic expression profile data by setting the parameters for size and color of the nodes and edges according to expression profile data of the genes (Fig 3). On visualising and analysing the genetic network merged with expression profile data elucidates most potent genes that could be very crucial in causing Alzheimer disease.

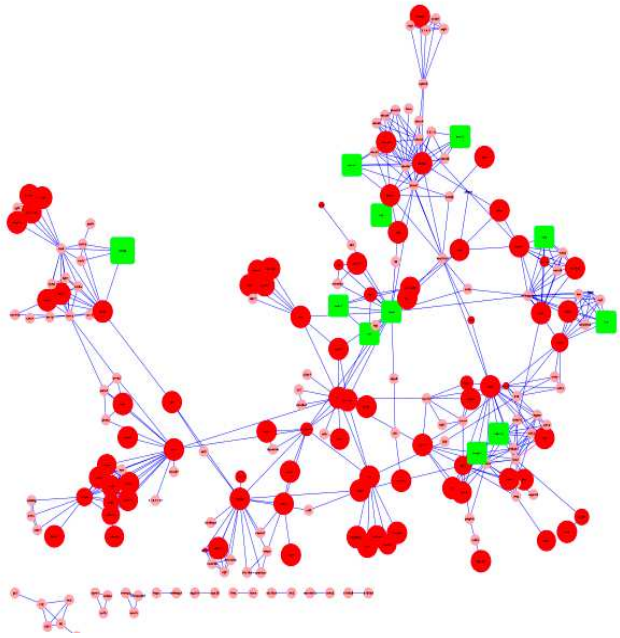

Fig 3: Network after merging genetic map

Result and Discussion:

Cytoscape is used for generating and visualising the genetic network involved in causing Alzheimer's disease. We tested the functional significance of differentially expressed 5-hydroxytryptamine (5HT) genes in causing Alzheimer's disease. We selected 14 candidate genes (5-HT1A, 5-HTR1B, 5-HTR1D, 5-HTR1E, 5HTR1F, 5-HTR2A, 5-HTR2B, 5HTR2C, 5-HT4A, 5-HTR4B, 5-HT5A, 5-HTR5B, 5-HT6 and 5-HT7) for building the genetic network involved in causing Alzheimer's disease. Fig 1. shows the normal genetic network before merging with genetic expression profile data whose edges and nodes colours and sizes parameters are set according to outdegree of each gene in the network. This network shows HTR1A, HTR2A, HTR6, BIN1, CR1 and APOE having maximum outdegrees distribution (Fig 4) and average clustering coefficient (Fig 5).

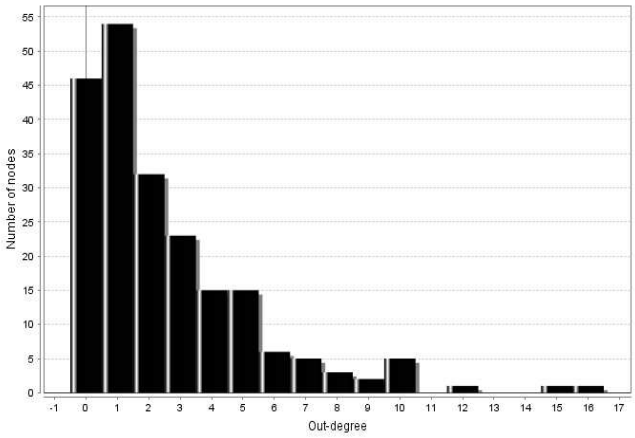

Fig 4: Outdegree distribution in the network

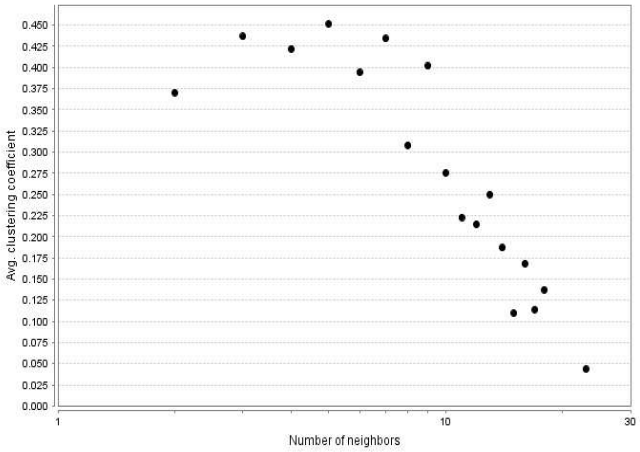

Fig 5: Average clustering coefficient distribution in the network

These results suggest a significant role of these genes in regulating the corresponding genetic network. Further we merged the expression datas for the genes in network to examine the variations induced due to changes in the expression values of corresponding genes. Genetic network merged with genetic expressions reveals the importance of 5-HTR2A,5-HTR2C and 5-HTR4 in causing Alzheimer disease which was further supported by the observation obtained through Enrichment map (with Jacard + overlap coefficient combined cut-off value = 0.375). Enrichment map categorized all the differentially expressed genes in Alzheimer disease on the basis of correlation of the genetic expressions. Among all correlated genes in the Enrichment Map HTR2A[3], PICALM[8, 9], CLU[8, 9], IN1[9], PDYN[10], ABCA8[11], HSP90AA1[12], GRIA2[13], APP[14], CAMKV[15],LRP2[16], PRDM2[17],MAP1B[18] ,BMP7[19] and MTM1[20] are previously reported to play significant role in causing Alzheimer disease. The result obtained in this study reports HTR2C as a significant candidate gene for Alzheimer disease. This methodological observation will provide a landmark for development of new drug targets against Alzheimer's.

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