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RESEARCH ARTICLE

PATHWAY MAPPING OF PROTEINS INVOLVED IN MULTIPLE SCLEROSIS AND IDENTIFICATION OF NOVEL PROTEINS

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ABSTRACT

WASH in the urban areas Multiple sclerosis is an unpredictable potentially disabling disease that causes disruption of the myelin that insulates and protects nerve cells of spinal cord and brain and permits electrical impulses to be conducted along the nerve fiber with speed and accuracy. So this disease disrupts central nervous system by damaging or demyelinating the insulated covers of nerve cells. In this paper we have made network of interacting proteins of more than 300 interacting proteins identified from protein interaction database .Initially 14 proteins were identified from Uni Prot database that were involved in multiple sclerosis disease . Gene Cards database was used to study pathways of proteins involved in network and new network was made that classifies interacting proteins on the basis of pathways involves. We found Three proteins, APBB2, APBB3 and MMP15 having no information about pathway and disease in which they are involved. New Network was designed to predicted pathway of these novel proteins, APBB2, APBB3 and MMP15, network mapping shows that these proteins connects directly to LRP4, that belongs to GPCR Signaling in Alzheimer's disease pathway. This suggests that these proteins are involved in multiple sclerosis and also other diseases like Alzheimer's disease. Further work can be done to identify potential drug target and can be used for drug designing.

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INTRODUCTION

Multiple – Many; Sclerosis – scar tissues or lesions. Multiple sclerosis is an unpredictable potentially disabling disease that causes disruption of the myelin that insulates and protects nerve cells of spinal cord and brain and permits electrical impulses to be conducted along the nerve fiber with speed and accuracy (Miller, 2008). So this disease disrupts central nervous system by damaging or demyelinating the insulated covers of nerve cells (Matusevicius, 1999). Due to this damage in the central nervous system, the ability of communication among the neurons by conducting nerve impulses is lost which may lead to various bodily dysfunctions (Fischer, 1999). It is a chronic disease having no cure as the progress, severity and specific symptoms of multiple sclerosis in any one person cannot be predicted (Mostert, 2002). As mentioned earlier, scleroses are scars like plaques or lesions in CNS. Due to inflammation and loss of myelin, transmission through nerves and various body functions are affected (Barcellos, 2003).

Types of multiple sclerosis: There are a number of distinct patterns relating to the course of the disease:-

- **Relapsing-Remitting Multiple Sclerosis:** Relapsing-remitting MS is the most common form of MS and typically occurs in young people. In this form of MS there are unpredictable relapses (exacerbations or attacks) during which new symptoms appear or existing symptoms become more severe (Poser, 1983). This can last for from days to months and there is partial or total recovery. The disease may be inactive for months or years. Approximately 85% of patients diagnosed with MS have relapsing-remitting multiple sclerosis (Bakshi, 2000).
- **Benign Multiple Sclerosis:** After one or two attacks with complete recovery, this form of MS does not worsen with time and there is no permanent disability (Flachenecker, 2002). Benign MS can only be identified when there is minimal disability ten to fifteen years after onset and initially would have been categorized as relapsing-remitting MS. Benign MS tends to be associated with less

severe symptoms at onset, for example, sensory (IFNB Multiple Sclerosis Study Group, 1993). Between 20% and 30% of patients diagnosed with MS have benign multiple sclerosis (Mäurer, 2000).

- **Primary Progressive Multiple Sclerosis:** This form of MS is characterized by a lack of distinct attacks, but with slow onset and steadily worsening symptoms (Jacobs, 1996). There is an accumulation of deficits and disability that may level off at some point or continue over months and years (Bradl, 2009). Approximately 10% of patients diagnosed with MS have primary progressive multiple sclerosis.
- **Secondary Progressive Multiple Sclerosis:** For some individuals who initially have relapsing-remitting MS, there is the development of progressive disability (i.e., nerve and muscle deterioration) later in the course of the disease often with superimposed relapses (Thompson, 1997). Approximately 40% of patients diagnosed with MS have secondary progressive multiple sclerosis (Ota, Kohei, 1990). Most patients suffer relapsing-remitting MS before it progresses to secondary progressive MS.
- **Progressive Relapsing Multiple Sclerosis:** This is a rare form of MS in which the disease is progressive from its initial onset (Kurtzke, 1983).

Table 1. Proteins involved in Multiple Sclerosis

S. No.	UniProt Id	Protein Id	Protein Name	Diseases
1	Q99497	PARK7	Protein deglycase DJ-1	Parkinson Disease 7, Autosomal Recessive Early-Onset and Park7-Related Parkinson Disease
2	P49768	PSEN1	Presenilin-1	Cortical Deafness and Mitochondrial Dna-Associated Leigh Syndrome and Narp
3	O75096	LRP4	Low-density lipoprotein receptor-related Protein-4	Frontotemporal Dementia with Parkinsonism-17 and Classic Progressive Supranuclear Palsy
4	Q9UHD2	TBK1	Serine/threonine-protein kinase	Severe Combined Immune Deficiency
5	P08575	PTPRC	Receptor-type tyrosine-protein phosphatase	Immunodeficiency Due to Cd25 Deficiency and Interleukin 2 Receptor Alpha Chain Deficiency
6	Q14790	CASP8	Caspase-8	Severe Combined Immune Deficiency
7	P16871	IL7R	Interleukin-7 receptor	Systemic Lupus Erythematosus 2
8	P02686	MBP	Myelin Basic Protein	Psen1-Related Dilated Cardiomyopathy and Early-Onset, Autosomal Dominant Alzheimer Disease
9	P03897	ND3	NADH-ubiquinone oxidoreductase chain 3	Cenani-Lenz Syndrome
10	P10636	MAPT	Microtubule-associated protein tau	Central Pontine Myelinolysis and Allergic Encephalomyelitis
11	P01589	IL2RA	Interleukin-2 receptor subunit alpha	No disease other than MS
12	Q15116	PDCD1	Programmed cell death protein 1	Amyotrophic Lateral Sclerosis 4 and Borna Disease
13	P01574	IFNB1	Interferon beta	Autoimmune Lymphoproliferative Syndrome
14	P19438	TNFRSF1A	Tumor necrosis factor receptor superfamily member 1A	Tumor Necrosis Factor Receptor 1 Associated Periodic Syndrome

Table 2. List of interacting proteins with proteins involved in multiple sclerosis

Proteins Of Multiple Sclerosis	Interacting Proteins	Databases used
PARK7	SNCA, CAMK1, TALDO1, ATP5J, PRDX2, NDUFA4, MTRF1, SLC18A2, EFCAB6,PINK1, PARK2, PTEN, MAP3K5, SUMO1, PRDX2, EFCAB6, MTA1, UBC	STRING, GeneMANIA ,DIP
PSEN1	NRG4, JAG2, ZNF274, NRG3, NRG2, FBXW11, NCSTN, DLL1, SRI, CTNND2, DNER, RPL10, DTNA, BACE1, PSENEN, PSEN2, APH1A, PKP4, CDH1, NOTCH1,APP, CTNNB1, APH1B, TRAF6, NOTCH3, GSK3B	STRING, GeneMANIA,DIP,MINT
LRP4	APBB2, MMP15, APBB3, APBB1, MMP14, APH1A, APH1B, PSENEN, NCSTN,DFNB31, PID1, MUSK, AGRN, SOST, DKK1, MINA, RASSF8, WNT7A, DOK7, LOXL2	STRING, GeneMANIA,DIP
TBK1	TICAM1, TLR3, IKBKE, IRF3, TRAF3, TLR4, IRF7, AZI2, HSP90AB1, HSP90AA1, TANK, TBKBP1, CDC42BPG, LETM1, ATG9A, HMMR, RBBP5, DDX58, TRAF2, UBC, TMEM173, MAVS,	STRING, GeneMANIA,DIP
PTPRC	LCK, HLA-DPA1, HLA-DOB, CD79B, HLA-DQA1, CD3E, CD3G, CD3D, SEMA4D, PAG1, CSK, DPP4, PRKCSH, GANAB,PTPRCAP, ITGAL, CD22, VAV1, FYN, ITGAM, ZAP70, CD4, SPI1, LYN, LGALS1	STRING, GeneMANIA,DIP
CASP8	BCAP31, FADD, CFLAR, RIPK1, PLEC, TNFSF10, TRADD, TRAF2, TNFRSF10B,EVA1C, NOD1, FAS, DAP3,TNFAIP3, SPP1, CEBPB,CASP9, TNFAIP8L2, CASP10,FASLG, TNFRSF10A	STRING, DIP, IntAct
IL7R	TSLP, IL7, IL2RG, SOCS2, JAK1, JAK3, SOCS4, SOCS7,PTK2B, TOE1, FYN, CRLF2,IL4, CBL, IL2	STRING, MINT, IntAct
MBP	PAK1, NFIC, CALM1, RPS6KA6, PHEX, HIPK2, ARHGEF5, APP, ROCK2, ROCK1, MPP2, PRMT10, PLP1, MAPK1, LRRK2, MAPK3, MAPK14, MAP3K5, MAG, PRMT5, PRKCA, PLP1, MAPK15	STRING, GeneMANIA,MINT
ND3	MT-ND4L, MT-ND4, MT-ND1, MT-ND5, MT-ND6, MT-ND2, NDUFV3,NDUFA11, NDUFB2, NDUFS5,NDUFB10, NDUFB4, NDUFA3,NDUFB9, NDUFA12, NDUFC2, NDUFB8, NDUFB11, NDUFA4, NDUFA13	STRING, GeneMANIA, IntAct
MAPT	CAMK2G, CAMK2A, CDK5, CAMK2D, CAMK2B, GSK3B, MAPK12, DYRK1A, PSEN1, FKBP4, STUB1, BAG1, HSPA8,AATF, UBC, FYN, MAPK8, MARK2,SNCA, PRKACA, YWHAZ	STRING, GeneMANIA, DIP
IL2RA	NMI, DOK2, SOCS1, CD3E, IL2RB,IL2, CREBBP, UGCG, CISH, SGMS1, TNFRSF9, IKZF3, TNFRSF18, TNFRSF4, ICAM1, EIF1, GATA1, CD4, IL2, IL2RB,IL2RG, CD4, STAT5B, IL7, STAT3,CD8A, TNFRSF18	STRING, GeneMANIA, IntAct
PDCD1	CD274, PDCD1LG2, PTPN11,CD8A, HLA-DRB1, LCK, CSK, CD3D, CD3G, CD3E	STRING, GeneMANIA, MINT
IFNB1	IRF3, IFNAR1, SOCS3, IFNAR2, IRF7, STAT1, IRF9, STAT2, IRF2, IRF1, IFNGR2, IFNGR1, DDX3X, IRF5, MAFB, HMGA1, CREBBP	STRING, GeneMANIA, DIP
TNFRSF1A	DAP, TRPC4AP, NRK, LTA, PIDD,TNIK, MAP4K2, TNFRSF1B, BIRC2, SMPD2, TNF, RFFL, RIPK1, NSMAF, CYLD, CYBB, NOX1, TRAP1	STRING, GeneMANIA,IntAct

- Symptom flare-ups occur and deterioration continues in between relapses (Confavreux, 2000). Approximately 5% of patients diagnosed with MS have progressive relapsing multiple sclerosis (Lock, 2002).

MATERIALS AND METHODS

UniProt database (UniProt Consortium, 2014) is used to identify proteins involved in multiple sclerosis and also to identify protein interaction data. Different other databases were used to identify interacting partners like STRING(19), Gene Mania (Warde-Farley,, 2010), DIP (Salwinski, 2004), IntAct (Kerrien, 2011) .Results were compiled in excel sheet and network was made using Cytoscape (Smoot, 2011) tool figure 1 shows the step wise methodology adopted to identify novel proteins involved in multiple sclerosis and its link to other pathways and diseases

RESULTS

Table 1 list the proteins involved in multiple sclerosis from retrieved from Uni Prot database and their interacting protein partners were identified using protein interaction database. Different database of protein interaction like STRING, DIP, MINT and Gene MANIA databases were used to find out interacting partners of proteins involved in multiple sclerosis as listed in table 1.

The interaction data from both the databases were downloaded in the form of excel sheet. Table 2shows the list of proteins that shows interaction with proteins involved in multiple sclerosis.

Network of proteins involved in multiple sclerosis: The excel files downloaded from databases, STRING, Gene MANIA, DIP and other databases as shown in table 2, were combined in a single excel sheetby making sure that each interacting protein appears only once in the excel sheet. The excel sheet was uploaded in Cytoscape software to create an interacting network. Figure 2shows the network that was created from list of interacting proteins Figure 2 color coding was done to differentiate query protein that is proteins involved in multiple sclerosis and their interacting proteins identified from databases. Blue color nodes are query proteins involved in multiple sclerosis and pink color nodes represent their interacting partners. These proteins were further studied to find out the pathway in which they are involved along with their related diseases using Gene Cardsdatabase (Stelzer, 2011). Network was classified according to pathway in which proteins are involved. Again new network was made as shown in Figure 3 shows the network of the interacting proteins classified on the basis of pathway in which they are involved. Color coding classifies proteins on the basis of their pathways. Detailed study of network was done to identify proteins directly linked to proteins of multiple sclerosis.

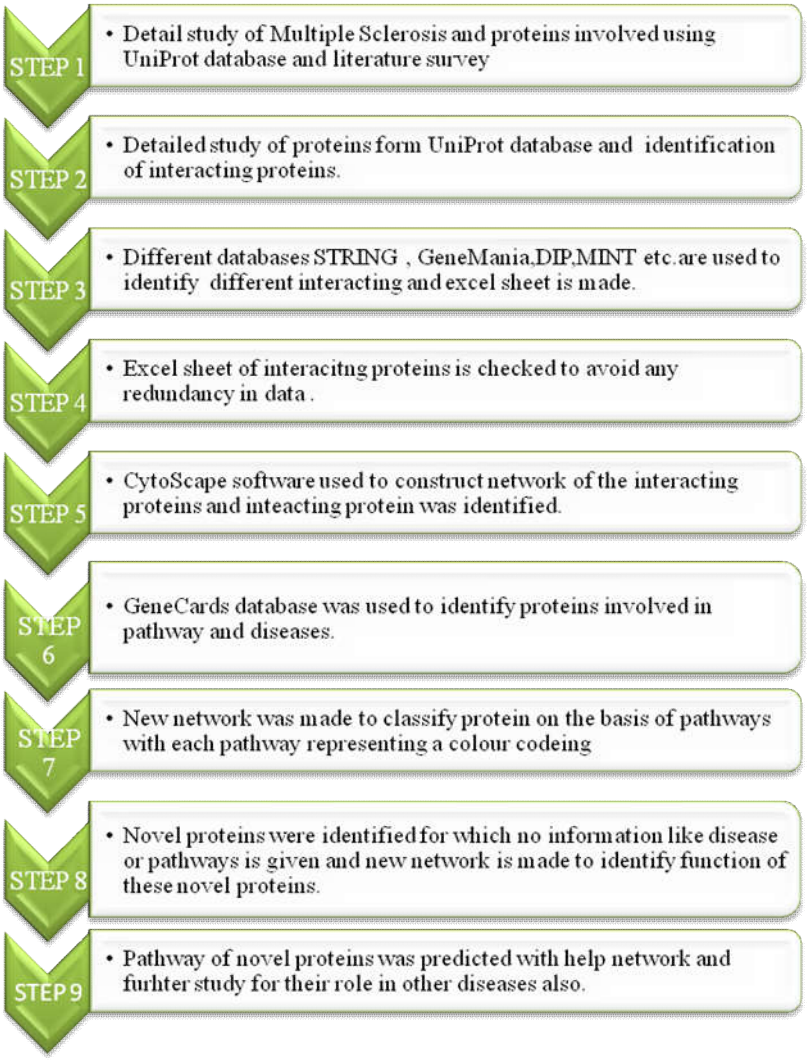

Figure 1. Methodology to identify novel proteins involved in multiple sclerosis

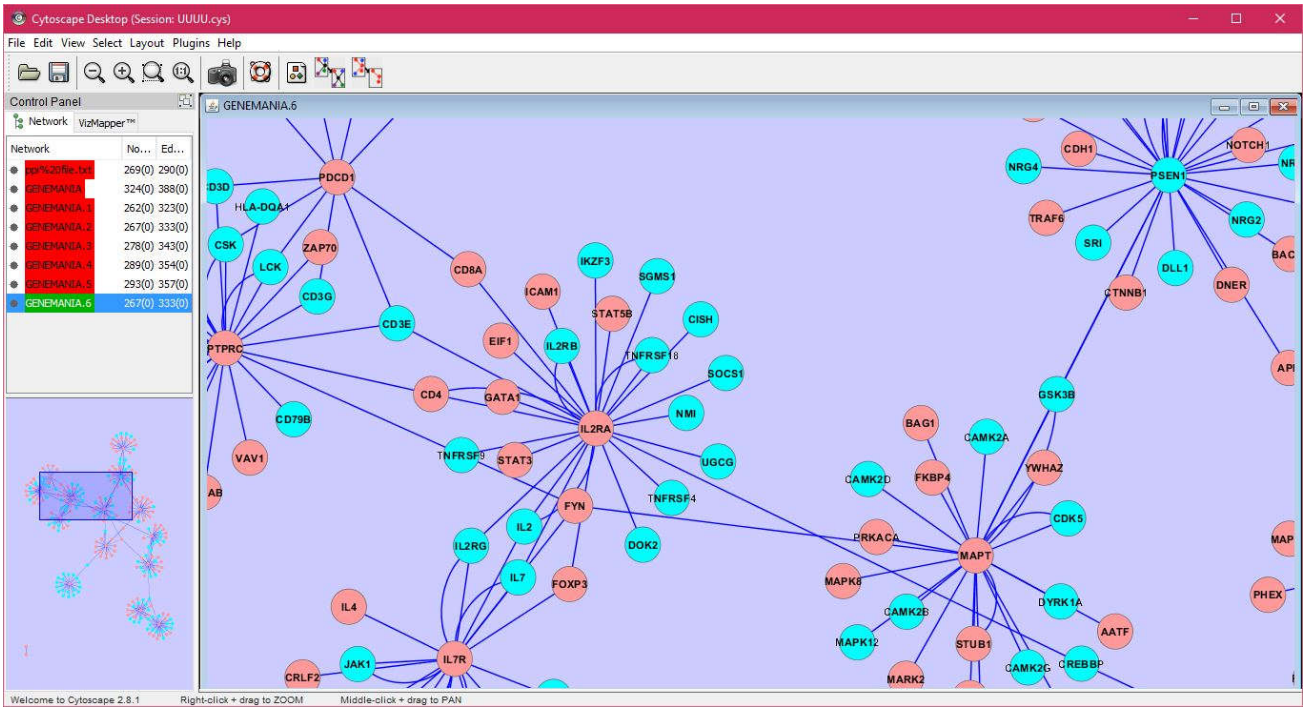

Figure 2. Proteins involved in Multiple Sclerosis (highlighted in blue) and their interacting proteins (pink nodes)

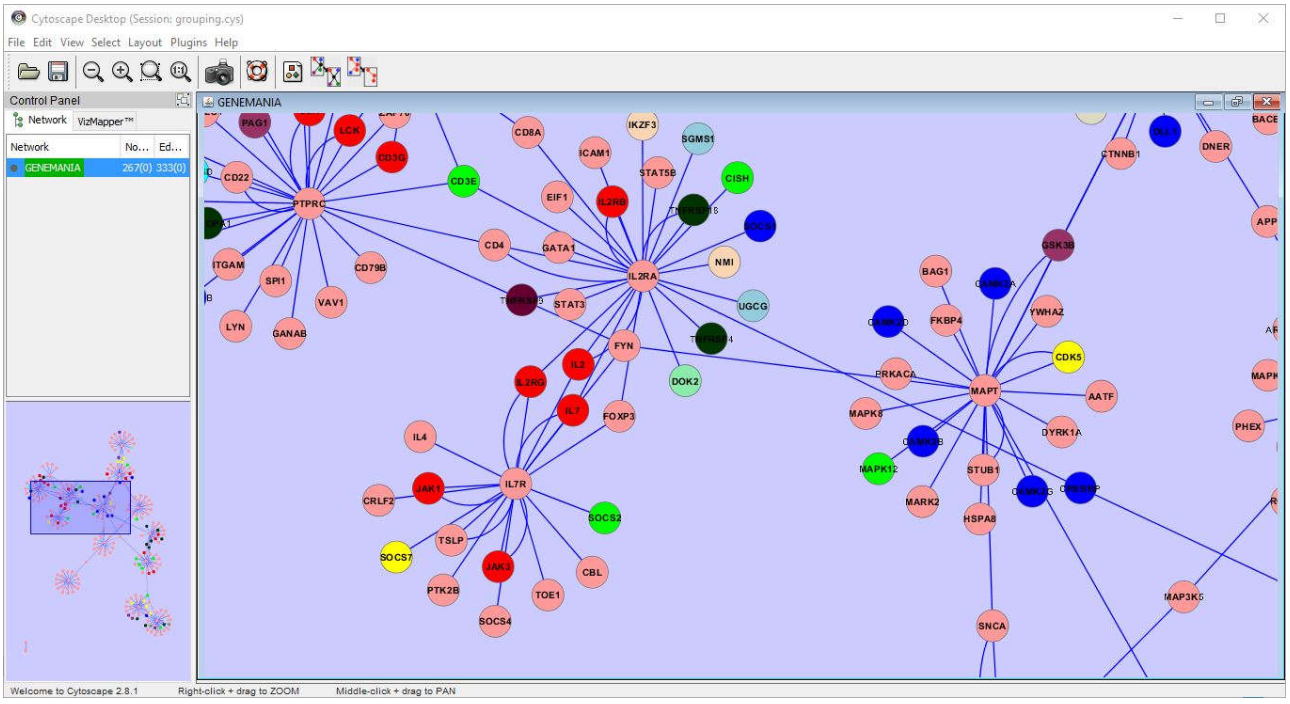

Figure 3. Proteins classified on the basis of their pathway (colors show different pathways)

	Immune System
	Signaling by GPCR
	PI3K/AKT Signaling Pathway
	Immune System and Signaling by GPCR
	Immune System, Interleukin receptor SHC signaling
	PI3K/AKT Signalling pathway and Immune system
	Tyrosine Kinases / Adaptors
	Degradation of the extracellular matrix, Adhesion
	Sphingolipid metabolism
	TNF signaling (REACTOME)
	IL-2 Pathway, IL2-mediated signaling events
	Ion Channeling
	Other pathways

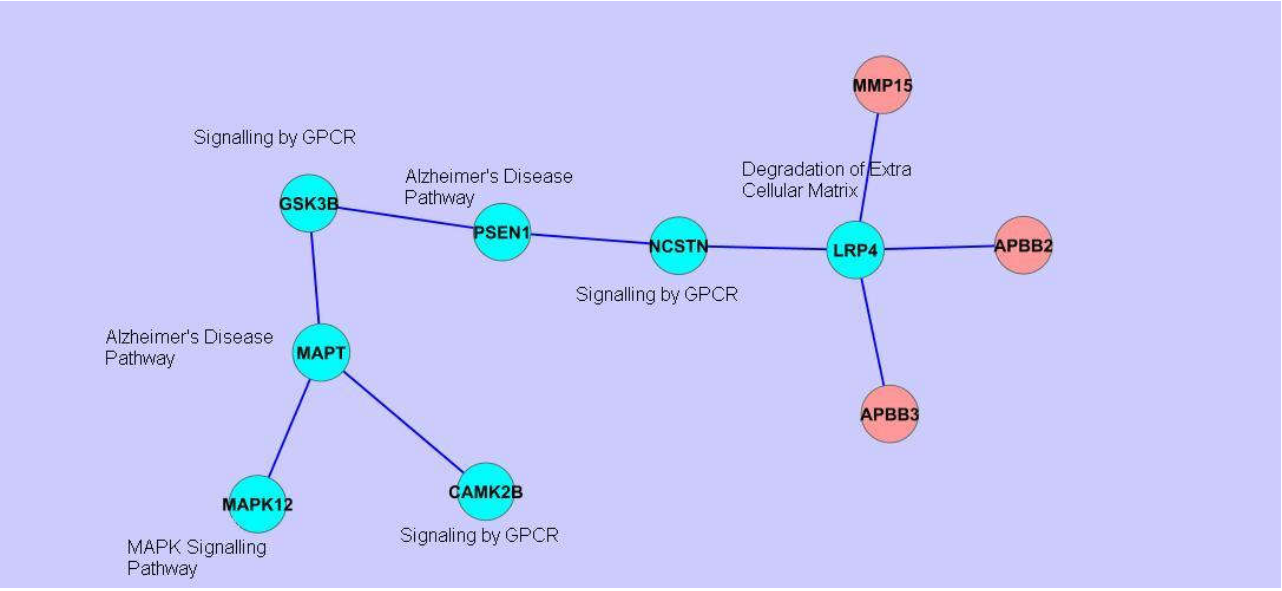

Figure 4. Novel Proteins involved in multiple sclerosis and pathway identification (MMP15, APBB2, and APBB3)

Three proteins (APBB2, APBB3 and MMP15) were identified having no information about their related pathway. New network was made for these proteins as shown in Figure 4 to identify pathways of these proteins .Figure 4 shows the network made in Cytoscape software in which all the three proteins, APBB2, APBB3 and MMP15, are connected linearly with LRP4 which is further connected to NCSTN, PSEN1, GSK3B, and MAPT and at the end, CAMK3B. Related pathways of the proteins are also mentioned in the figure.

DISCUSSION AND CONCLUSION

Out of several interacting proteins, three proteins were identified having no evidence of being involved in any disease or pathway. Those proteins were APBB2, APBB3 and MMP15.

APBB2 is amyloid beta precursor protein binding family B member 2(Li, 2005). With the cytoplasmic domain of the protein name, the protein encoded by APBB2 interacts (Tucsek, 2013). There are two phosphotyrose ring binding (PTB) domains which are assumed to function as signal transduction (Rutgers, 2011). Its polymorphic form APP is associated with Alzheimer's disease (Aarsland, 2009).

APBB3 is amyloid beta precursor protein binding family B member 3. It is multiple variant isoform of APBB2 so it has same function like its isoform (Miyake, Kunio, 2011).

MMP15 is matrix metallopeptidase 15 (Lin, 2013). It belongs to a peptidase M10 family which is involved in the breakdown of various physiological processes (Abraham, Reimar, 2015). Members of this subfamily contain a transmembrane domain suggesting that these proteins are expressed at the cell surface rather than secreted (Asano, 2008). The encoded preproprotein is proteolytically processed to generate the mature protease (Hiden, 2007). In Figure 4, APBB2, APBB3 and MMP15 are directly connected with LRP4 which is further linearly connected with PSEN1 followed by GSK3B then MAPT and the linear chain terminates at CAMK2B. The figure clearly depicts that proteins from LRP4 to CAMK2B are either involved in GPCR Signaling or Alzheimer's disease pathway.

So the predicted pathways of the three protein- APBB2, APBB3 and MMP15 can be GPCR Signaling involved in Alzheimer's disease pathway and also involved in multiple sclerosis disease. Further study is required to study the role of these protein in diseases and their mechanism.

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