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PATHWAY CONSTRUCTION OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIPD): A NEURODEGENERATIVE DISEASE

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ABSTRACT

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is a form of peripheral neuropathy, often difficult to diagnose. It's an auto immune disorder, due to subtle occurrence, this disease is not much studied and mostly people are unaware of symptoms and cause. In this paper protein interaction map has been constructed that shows the relationship of CIDP disease with other neurological diseases and also nature of protein interaction. The proteins responsible for the disease (CIDP) were identified using extensive literature survey, Uni Prot and KEGG databases. Protein interaction map was constructed with the help of different softwares like Cytoscape, Gene MANIA, String, Pathway common and Biocarta. The protein interaction map of CIDP shows the nature of protein interaction such as Physical interaction, Neighbor hood, Co- expression, Pathway, Co-localization etc. This protein interaction map of CIDP and protein relatedness with other neurological disease might serve as a source of information to develop new drug targets and a potential cure or control for the neural disease.

INTRODUCTION

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) is an auto immune disorder which affects the peripheral nervous system of Human body (Peripher, 2015). CIDP is chronic form of Guillain-Barre syndrome. CIDP occurs due to immune cells, which are assigned to protect our body from foreign materials but in this case, it instead attacks the nerve cells and as a result the nerve cells fail to response to any stimuli or respond weakly. This causes numbing, tingling, pain, progressive muscle weakness loss of deep tendon reflexes fatigue and unusual sensations. The chances of progression of this disease are very high (Mori, 2002).

Mechanism of Chronic Inflammatory Demyelinating Polyneuropathy

Researcher has successfully proposed the mechanism of CIDP disease study suggest that in Demyelinating Polyneuropathy a pre-existing infection evokes an immune response, in turn it cross reacts with peripheral nerve components because of the sharing of cross- reactive epitopes this phenomenon is usually referred as molecular mimicry, this results in Acute Inflammatory Demyelinating Polyneuropathy (Guillain-Barre syndrome) (Hafer-Macko *et al*., 1996). Further the immune response is directed towards the myelin (epitopes of Schwann cell surface membrane) or the axon of peripheral nerve, inflammatory demyelination starting at the level of the nerve roots (Nicolas and Guillaume, 2002). The earliest changes are often seen at nodes of Ranvier. As this disease progresses, it completely destroys the myelin sheath, the outer covering of nerve cells, that protects the nerve cells and helps in conduction and transmission of signals and this results in the chronic form of AIDP i.e., Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (Berger and Alan, 2003).

CIDP symptoms

CIDP is difficult to diagnose as the symptoms are not so well differentiated, the symptoms must be present for at least two months and the most likely symptoms of CIDP are symmetric weakness of both muscles around the hip and shoulder as well as the hands and feet (proximal and distal muscles) this pattern

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of weakness is highly suggestive of CIDP, even motor functions are altered. The tests that can be a help for diagnostics include nerve conduction testing and electromyography, looks for very slow conduction velocities, lumbar puncture looking for elevated spinal fluid protein without many inflammatory cells and MRI imaging of nerve root is done to look for any enlargement or signs of inflammation (Köller and Hubertus, 2005). All these diagnosis helps, but most of the time this disease goes un-noticed. This rare disease affects any age group and its onset may begin at any decade of life. CIDP affects males twice as often as females and the average age of onset is 50. The prevalence of CIDP is estimated to be around 5-7 cases per 100,000. Due to its subtle occurrence this disease was not much in focus, but the recent outbreak of Zika virus in Brazil, mainly affecting the growing embryo of humans causing neural problems and one of the neural problems reported was Guillain-Barre syndrome (AIDP) the acute form of CIDP, this outbreak has implemented a lot of lime light towards the study and research of the disease (Roa, 1994)

Proteins Involved In CIDP

As we know that the proteins play a crucial role in expression of any disease, identification of these proteins are very important so that the disease can be managed or controlled. Many a times these proteins become the potential drug targets and helps in curing the disease. Analysis of pathway of these proteins helps in blocking their formation or metabolism. So following are the proteins involved in CIDP (www.UniProt.org). The following information related to the proteins was taken from UniProt. This information helps in understanding their use, occurrence, and importance in human body. Table 1 list the different proteins involved in CIDP and also involved in other neurological diseases.

Uniprot

It is the universal protein resource, complete and comprehensive resource of proteins containing all required data about protein to annotate it. The UniProt databases are the UniProt Knowledgebase (UniProtKB), the UniProt Reference Clusters (UniRef), and the UniProt Archive (UniParc) (www.UniProt.org/UniProt). Proteins associated with CIDP is retrieved from UniProt database and disease associated with each disease is studied.

GeneMANIA

It helps in predicting the function of the desired genes and sets of gene. It finds other genes that are related to the set of input genes, using a very large set of functional association data. The association data contains protein and genetic interactions, pathways, co-localization, co-expression and protein domain similarity. It can be used to find new members of a pathway or complex, in addition finds genes which might have been missed on screen by the user. GeneMANIA is actively developed at the University of Toronto, in the Donnelly Centre for Cellular and Biomolecular Research in the labs of Gary Bader and Quaid Morris. GeneMANIA allows user to upload his/her own data in the form of Text Tab (Delimited) file and can visualize the results in the form of network constructed by the software using the user uploaded data (www.String-db.org). Fig.1. shows the protein interaction map from GeneMANIA all proteins involved in CIDP are studied in GeneMANIA to identify their interacting partners and also to classify type of interaction

STIRING

This database provides the user with a critical assessment and integration of protein-protein interactions including direct (physical) as well as indirect (functional) interactions and associations. STRING covers more than 2000 organisms. It provides the users with all the protein –protein interactions, it have the hierarchical representation of the proteins.

Table 1. Protein Associated with CIDP

S.No.	Protein ID	Protein Name	Diseases
1	PMP-22	Peripheral myelin protein-22	Charcot- Marie- tooth (CMT), Dejerine- Sottas syndrome, Hereditary neuropathy with pressure palsies.
2	NAGLU	Alpha- N- acetyl glucosaminidase	Mucopolysaccharidosis3B
3	PRPS1	Ribose- phosphate pyrophosphokinase-1	Charcot- Marie- tooth 2V,Charcot- Marie- tooth X5,ARTS Syndrome
4	LRSAM1	E3 ubiquintin protein ligase	Charcot- Marie- tooth 2P
5	SLC25A19	Mitrochondrial thiamine pyrophosphate carrier	Microcephaly
6	SH3TC2	SH3 domain tetratricopeptide repeat containing protein -2	Charcot- Marie- tooth 4C Mononeuropathy of median nerve
7	DMXL2	DMX like protein-2	Polyendocrine, polyneuropathy syndrome
8	MPZ	Myelin protein PO	Charcot- Marie- tooth 1B Charcot- Marie- tooth 21 Charcot- Marie- tooth 2
9	VCL	Vinculin	Neuropathies

This database also provides with the 3-Dimensional structure of proteins and all the required information to annotate the proteins. (www.pathwaycommons.org). Fig.2. shows the protein interaction map from string database .All protein that are involved in CIDP are also studied in string database to identify protein interaction.

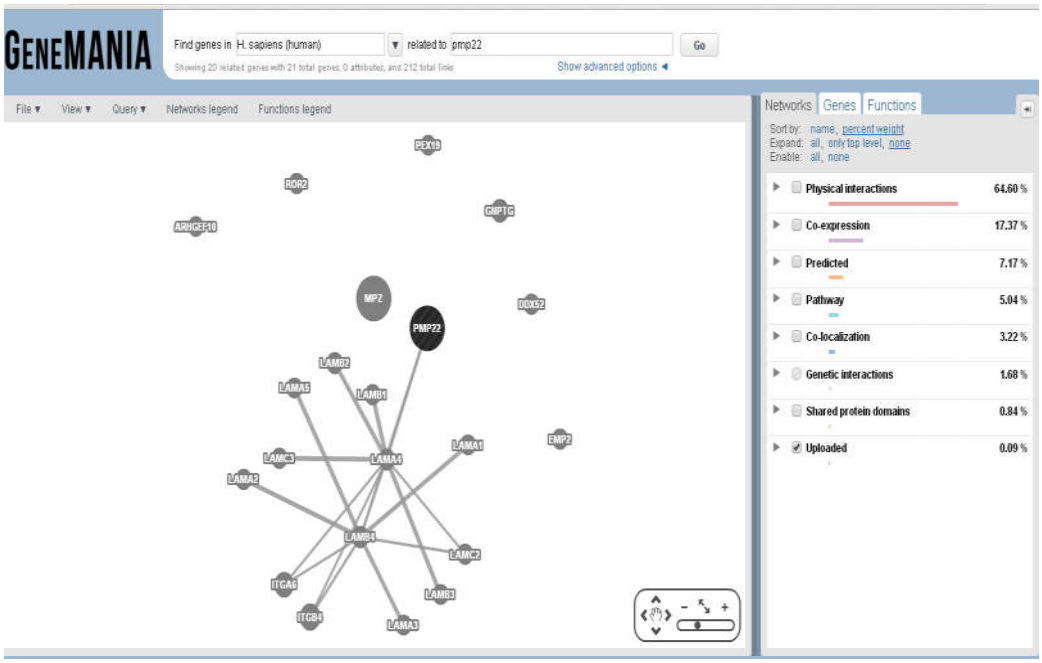

Fig. 1. Protein interaction map from GeneMANIA

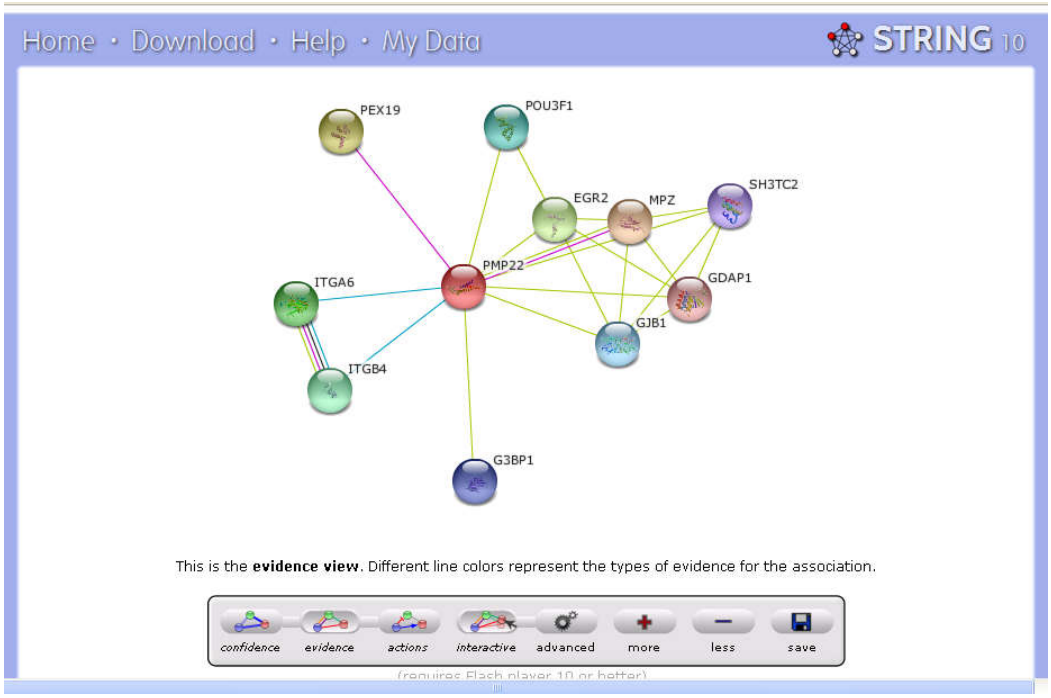

Fig. 2. Protein interaction map from string database

Pathway Commons

It is also a resource of network biology which acts as a convenient place to access various biological pathways, the information of these pathways are collected from public pathway databases. These pathways can be easily searched, visualized, and downloaded. **(**www.cytoscape.org**).** It is open source software for visualizing molecular networks and biological pathways and integrating the networks with information, gene expression profiles and many other data.

The core function of cytoscape is data integration, analysis and visualization. Some additional features are provided available as App (plugins) for providing the user with new innovational layouts, network and molecular profiling analyses, wide range of file format support and connecting with new refined databases for correct and accurate results. The result is in a form of network and this network can easily be analyzed and a lot of information can be obtained. The network obtained can be completely annotated and be used for any future purpose.

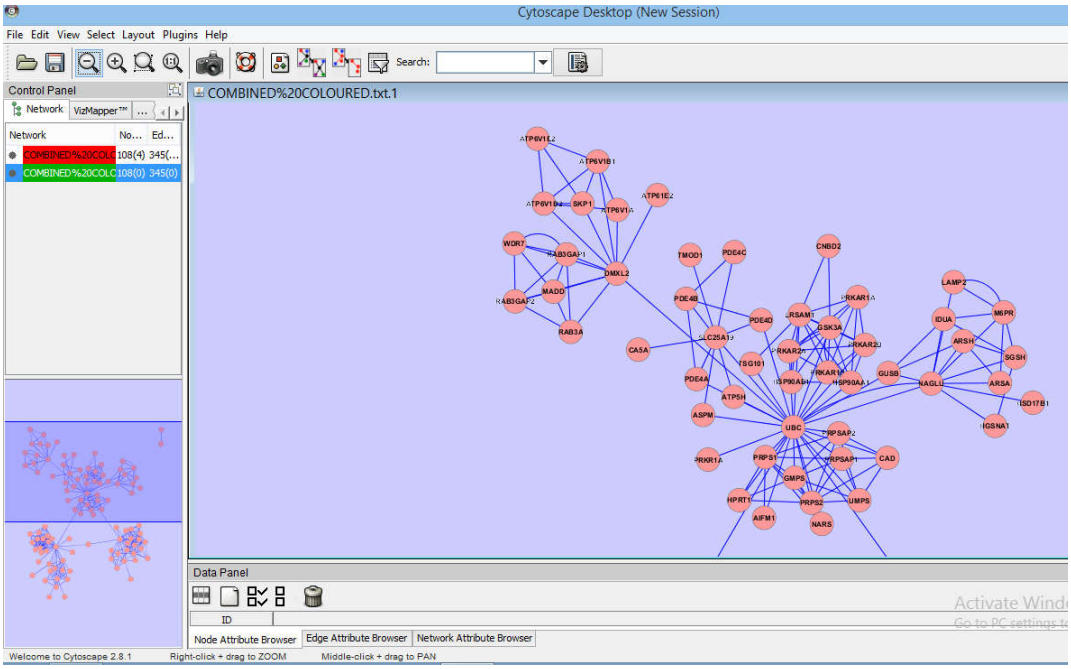

Fig. 4.Protein interaction network constructed by cytoscape

Table 1. Interacting Proteins with CIDP proteins

S.No.	Proteins of CIDP	Interacting proteins	Database
1	PMP22	LAMB4,LAMB2,LAMA2,LAMA3,LAMB3,LAMC2,LAMA1,LAMA4,LAMB1,LAMA5,LAMC3,ITGA6,ITGB4,MPZ,PEX19,UBC,POU3F1,GJB1,G3BP1,SH3TC2,GDAP1	GeneMANIA& String
2	NAGLU	HGSNAT,GUSB,SGS,IDUA,HSD17B1,M6PR,ARSH,LAMP2,ARSA,UBC	String
3	PRPS1	PRPSAP1,UBC,PRPS2,PRPSAP2,A1FM1,UMPS,HPRT1,NARS,GMPS	String
4	LRSAM1	TSG101,UBC,HSP90AA1,HSP90AB1,GSK3A,PRKAR1B,PRKAR1A,CBND2,PRKAR2B,PRKAR2A	String
5	SLC25A19	ATP5H,PDE4D,PDE4A,PDE4B,PDE4C,ASPM,TMOD1,CA5A,UBC	String
6	SH3TC2	NDRG1,PMP22,GDAP1,FGD4,SBF2,CTDP1,MPZ,MTMR2,ATP7A,KRT86	String
7	DMXL2	RAB3GAP1,WDRT,RAB3GAP2,SKP1,ATP61A,MADD,RAB3A,ATP61B1,ATP61B2,ATP61E2,UBC	String
8	MPZ	PMP22,GJB1,K1F1B,MPZL1,PES1,MED25,MFN2,EGR2,MTMR2	String
9	VCL	CTNNA1,MYO6,CTNNA2,CTNNA3,CTNNAL1,MYH11,LMOD1,SORBS1,PTK2,PXN,TLN1,ITGB5,ITGA1,SORBS3,CALD1,SRC,UBC,RAVER1,TNS1,ACTN1,CIRBP	GeneMANIA& String

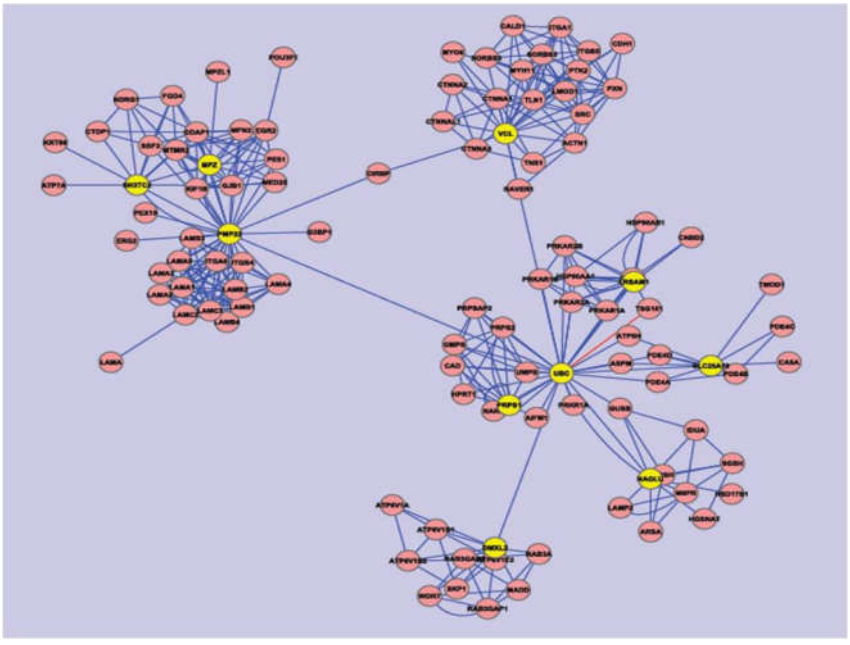

Fig. 5. Protein interaction map of CIDP proteins yellow nodes represents the CIDP associated proteins

Table 3. Protein –protein interaction file format

Gene ID	Gene ID	Score	
LAMB4	LAMC2	1	
LAMB4	LAMA3	1	
LAMB4	LAMA1	1	
LAMB4	ITGB4	1	
LAMB4	ITGA6	1	
LAMB4	LAMA4	1	

The network can be saved in PDF format. Cytoscape can be easily downloaded from (http://www.cytoscape.org/) current version cytoscape 3.4.0 is used to construct protein network. (Yoon *et al*., 2006). Cytoscape was used for making the final pathway with complete annotation fig.4. shows the protein interaction network in cytoscape software. The interactions were uploaded in the form of Text Tab (Delimited) file and analyzed in cytoscape (Newman, 2003).

MATERIALS AND METHODS

The proteins were identified using UniProt database, and UniProt id list is created to study protein interaction in differ rent databases. The proteins identified were searched on different pathway databases such as GeneMANIA and String using the unique ID provided by UniProt (Brandes, 2001).These pathway databases gave all the interactions of the particular protein. These interactions were well annotated and a table was constructed using Microsoft Excel, in this table the different proteins interacting with the main protein and the several other proteins were entered with a score which indicated the strength and existence of the interaction. The excel file contained three columns the first column contained the interacting protein, the second column contained target protein and the third column contained score of interaction which ranged from 0-1. If the score is 0 it means the interaction is very weak and if the score is greater than 0 and less than 1 then the interaction ranges from weak and moderate.

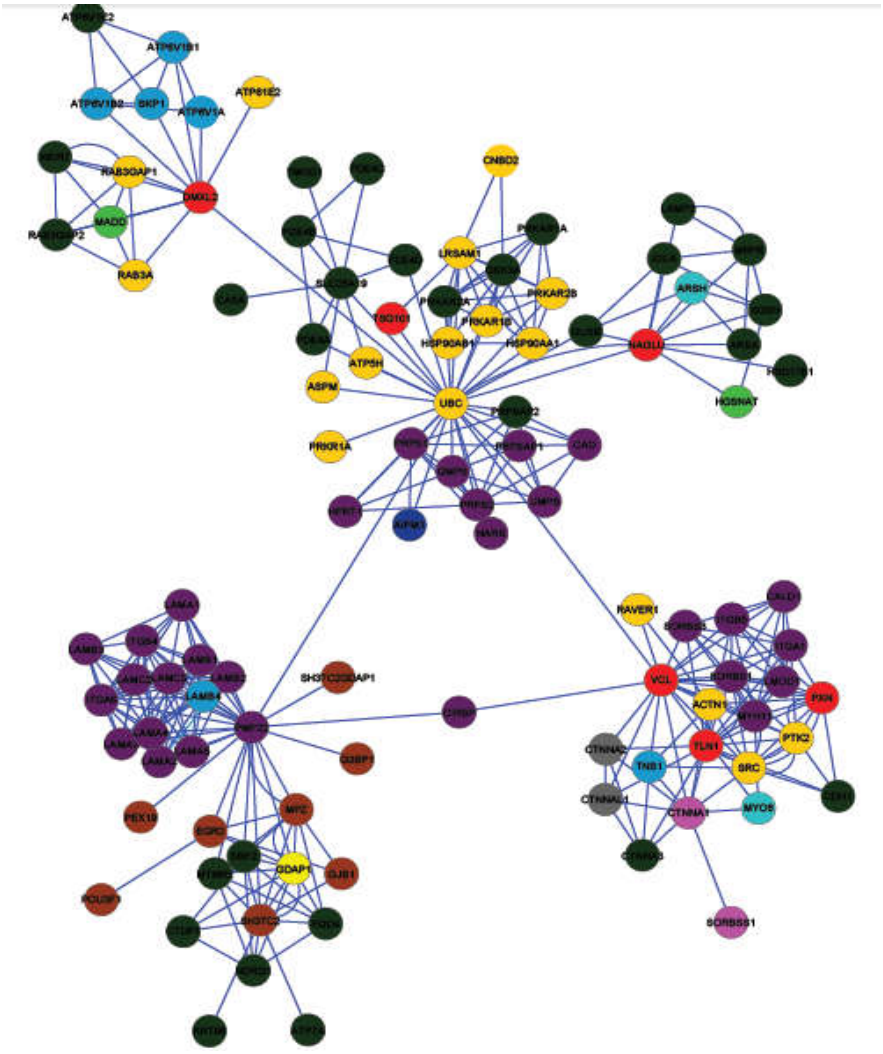

Fig. 6. Protein Interaction Map of CIDP Proteins Different Node Color Represents Types of Protein Interaction

	Physical interaction		Shared protein domain		predicted
	Neighbor hood		Text mining		Database
	Co- expression		Experimental		Co- occurrence
	Pathway		Co-localization		All

The score 1 indicates that either the interaction is very strong or doesn't exist. This tab delimited file was uploaded on cytoscape the tool used for the construction of the pathway. The result obtained was a full interacting network. The network obtained was annotated and was analyzed (Shimbel, 1953).

RESULT AND DISCUSSION

Protein interaction data from GeneMANIA and String

Networks or pathways of cell signaling and metabolic reactions from different databases are defined by different levels of detail and information provided by the database. Details provided may include proteins, small molecules, DNA, RNA, complexes and their cellular locations different types of interactions such as cellular molecular, physical, co-expression etc. these databases provided us with ample and sufficient amount of information and different interaction of the particular protein.(Mick *et al*., 2010).TABLE 2 shows the protein interaction data of protein involved in CIDP and source database

Protein-Protein Interaction File Format

The file which was imported in cytoscape for the final result consisted of three columns. The first two columns consisted of interacting proteins and the third column consisted of score of the interaction. The score was in between 0- 1, 0 represented that the interaction doesn't exist and values above 0 represented the strength of interaction like weak, moderate, strong and very strong. The value of 1 represented either very strong interaction or not sure about the interaction. The file was constructed in Microsoft excel and saved in tab text (delimited) form (Veyrieras *et al*., 2008).TABLE 3 shows the protein interaction file format.

Construction of Protein Interaction Map using Cytoscape

The above excel file was uploaded and the result was analyzed using the network analyzer tool in cytoscape and the reliability of network is studied. Fig 5 shows the constructed network in cytoscape where colored nodes indicate the proteins involved in CIDP and its interacting proteins. The network was visualized in various patterns but the final network was generated on the basis of the protein interaction score (http://med.bioinf.mpiinf. mpg.de /netanalyzer/help/2.7 /index.html#simple.). Fig 6. Shows the network with colored nodes indicates the type of interaction and database used for generating this network (Po elmans *et al*., 2011). Fig .6. Shows the protein interaction network of CIDP. The protein interactions were analyzed and type of protein interaction was studied, different nodes color indicates the different in protein interaction types like Physical interaction Neighbor hood, Co-expression, Pathway, Shared protein domain, Text mining, Experimental, Co-localization.

Conclusion and Discussion

The pathway constructed was integrated on the basis of top findings of proteins involved in the CIDP, using the UniProt database.

Findings revealed that the 9 proteins which were identified had other interacting proteins which interacted with each other and formed a network the total interactions shown were around 100. These proteins are not only involved in CIDP but are a part of many other Neurodegenerative disorders. The data was retrieved from different databases, proteins are integrated on the basis of Physical interactions, Neighborhood, Co-expression, Pathway, Co-localization, Shared protein domain, Text mining, Experiments, Co- occurrence, predicted. The protein signaling pathway of CIDP was identified, this disease destroys the nerve fibers and the alteration in the signals given by these proteins supports the disease. As all the neurological disorders are connected one disease may lead to another disease and finally can form more complex disease that is a syndrome. The proteins identified using different database and studies suggested that these 9 proteins are directly involved and contributes to the neuropathies the other interacting proteins may help us to regulate the expression of the major proteins, these proteins may serve as a potential drug targets and help in advancement and development of personalized medicine. The identified protein network for CIDP contributes to our understanding of the molecular basis of the disorder. In addition, the data suggest new candidate proteins for CIDP and provide clues to future research of CIDP treatments. These pathways might be useful in clinical purposes such as the prediction of disease, prognosis of disease, identification of new treatments, potential drug targets and new strategies to tackle the disease.

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