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Bioinformatics Approach for Pattern of Myelin-Specific Proteins and Related Human Disorders

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Abstract

Background: Recent neuroinformatic studies, on the structure-function interaction of proteins, causative agents basis of human disease have implied that dysfunction or defect of different protein classes could be associated with several related diseases.
Objectives: The aim of this study was the use of bioinformatics approaches for understanding the structure, function and relationship of myelin protein 2 (PMP2), a myelin-basic protein in the basis of neuronal disorders.
Methods: A collection of databases for exploiting classification information systematically, including, protein structure, protein family and classification of human disease, based on a new approach was used. Knowledge discovery was carried out based on collections criteria and in silico integrative in vitro studies.
Results: The results of the evaluation of bioinformatics comorbid proteomics studies revealed that PMP2, an intracellular and membrane myelin protein, is specific for a neuritis disease and collaborative to other diseases. Leprosy, another neuronal disease that could be related to neuritis, consists of interferon gamma (IFNG), a secreted protein included various protein classes from what is neuritis.
Conclusions: The growth rate of information in bioinformatics databases could facilitate studies of live organisms prior to observation studies. Two different protein classes could be causative agents of one disease. However, two related diseases from one disease group could consist of different protein classes. Future research in the field of proteomics could allow modern insight to reshuffling of proteins in different diseases, and lead to the discovery of the etiology of such diseases.

Keywords: Bioinformatics Databases, Myelin Protein 2 (PMP2), Protein Classes, Human Disorders

1. Background

The myelin sheath is a dynamic entity multilayered membrane in the vertebrate nervous system that is produced by and extends from Oligodendrocytes (OLG) including the lipid-rich (approx. 70% of its dry weight) (1, 2) several hundreds of proteins (3), and has unique biochemical properties (4).

In the past decades, advances of bioinformatics tools in the study of proteomics marked the beginning of a quiet revolution of biological investigation, in which researchers systematically studied organisms on different levels, including genomes (5), transcriptomes (6), proteomes protein expressions (7), metabolomes (8) and interactomes (9). Since, most physiological and pathological processes are manifested at the protein level, biological scientists are rapidly becoming interested in applying proteomic techniques in combination with bioinformatics studies to foster a better understanding of basic molecular biology, for numerous diseases (10, 11) and protein levels, and they can give a fairly complete view of living organisms (12-14).

Recent studies have implied that myelin biogenesis is a carefully regulated process, related to the presence of a group of proteins neuro-targets, which are mainly expressed by myelinating cells in myelin sheath. They are generally thought of as “myelin-specific protein” (15, 16) and are located in the central nervous system (CNS) and peripheral nervous system (PNS).

Myelin protein 2 (P2) or peripheral myelin protein (PMP2) is a “myelin-specific protein” in the basis of neuronal disorders with high abundance in PNS myelin (17). Although, detailed P2 membrane-binding mechanism is unknown; its structure in different species, by biochemical techniques is known (18).

The structure-function studies of this protein revealed

that a small, basic (19) and a peripheral membrane protein, as it is a fatty acid binding protein (FABP) including lipid transport myelin (17). Moreover, it is the crucial antigen involved in the induction of experimental allergic neuritis, which is an autoimmune disease of the peripheral nervous system (20).

Evidence observation with consolidate basis displayed that intravenous administration of 100 microgram of recombinant P2 protein twice daily, could completely prevent experimental autoimmune neuritis induced by adoptive transfer of neuritogenic P2-specific T cells or by immunization with the neuritogenic P2-peptidespanning amino acids 53 - 78 (21).

The human PMP2 gene was allocated to chromosome 8q21.3-q22.1 (19), as a candidate gene for autosomal recessive Charcot-Marie-Tooth disease type 4A (18, 22).

There are various distinct PMPs, thrombin-induced PMP-1 [tPMP-1], PMP-2 and human neutrophil defensin-1 (hNP-1), which are accomplished with membrane damage with different mechanisms (23). Exonic Single nucleotide Polymorphisms (SNPs) at positions 220 (A/G) and 445 (C/T) of the peripheral myelin protein 2 (PMP2) (24) are described with the application of single-strand conformation polymorphism (SSCP) analysis (25, 26). In addition, using SSCP and physical map, has demonstrated that the myelin protein PMP-2, mapped by fluorescent in situ hybridization (FISH) to transformation region in acute transverse myelopathy (ATM), is not the defect in CMT4A (25-27). Lymphocytes from patients with acute ATM were shown to undergo a specific and significant transformation when cultured in vitro in the presence of either the central nervous myelin basic encephalitogenic protein or the peripheral nerve myelin P2 protein (20).

In the past decade, evidence based on experimental observation of the disease related to PMP2, revealed that this myelin-specific protein could be highly related to neuritis disease.

Neuritis, a general inflammation of the peripheral nervous system, and sensorineural hearing loss is associated with an important gene, PMP2; affiliated tissues include T-cells and brain. Neuritis is characterized by different nerve symptoms including pain, paresthesia, paresis, hypoesthesia, anesthesia, paralysis, wasting and disappearance of reflexes. Physical and chemical injuries, comorbid environment factors and collection of disease have been considered as causes of neuritis (28). Moreover, neuritis consists of four types of clinical features including brachial, cranial, optic and vestibular neuritis (29). Also, this neuronal disease is related to a collection of family proteins, which may be considered as an etiology of disease.

Leprosy, a neural and infectious disease, could be transmitted by aerosol spread from infected nasal secretions to exposed nasal and oral mucosa. The types of infection leprosy include lesions in superficial peripheral nerves, skin, mucous membranes of the upper respiratory tract, anterior chamber of the eyes, or testes. Interferon Gama, a family of secreted proteins, is associated with Leprosy (30).

2. Objectives

The focus of this study was on bioinformatics approaches for understanding the structure, function and relationship of Myelin Protein 2 (PMP2), with other protein families, assumed to be involved in the basis of neuronal disorders.

3. Methods

The basic method in this study was the application of bioinformatics databases and tools. We used the following databases to predict peptides' protein structure, human disease, proteomic peptide analysis and reciprocal proteins: Expasy, HPRD, KEGG, NCBI, OMIM, PDB, PeptideAtlas, and UniProtKB. Moreover, a set of documents related to protein classes, myelin proteins, and neural disease were evaluated.

Since application of databases is emphasized to search queries and knowledge making is restricted to in vivo studies. In this study, there was an emphasis on databases that were effective for the exploitation of hypothesis including suitable quires and appropriate criteria. Researches have been carried out through gathering information and queries including the new in silico approach and then in vitro studies prior to in vivo investigation.

A categorized list of proteins and diseases based on theoretical frameworks interpretation was proposed including databases name, data type, contents, scope and methodology, as identified from different databases (Table 1).

4. Results

Evolving bioinformatics tools based on experimental experiences were identified in different bioinformatics databases; exploiting of these information revealed that the PMP2 could be related to different diseases. Priority based on average scores in different databases such as Z score was determined. This score was used as a confidence value to interpret linkage rate of these proteins with other diseases.

These diseases included neuritis (5.9), microsporidiosis (4.9), Pseudomyxoma peritonei (2.5), acute disseminated encephalomyelitis (2.3), Charcot-Marie-Tooth disease (2.2), mumps (1.8), demyelinating polyneuropathy

Table 1. Web Services Used in This Study

Name	Data Types	Brief of Content, Scope and Methodology	URL
Expasy, Expert Protein Analysis System	A wide range of resources in many different domains and areas such as bioinformatics	Expert Protein Analysis System and Swiss Institute of Bioinformatics (SIB) acted as a proteomics server to analyze protein sequences and structures.	https://www.expasy.org/
HPRD, Human Protein Reference Database	Centralized platform to visually depict and integrate information pertaining to domain architecture Protein-protein interaction	Human Protein Reference Database represented a centralized platform to visually depict and integrate information pertaining to domain architecture, post-translational modifications, interaction networks and disease association for each protein in the human proteome. All the information had been manually extracted from the literature by expert biologists who read, interpreted and analyzed the published data.	http://www.humanproteinpedia.org/
KEGG, Kyoto Encyclopedia of Genes and Genomes	Bioinformatics resource for deciphering the genome	The Kyoto Encyclopedia of Genes and Genomes presented a collection of disease entries capturing knowledge on genetic and environmental perturbations.	http://www.genome.jp/kegg/disease/
NCBI, National Center for Biotechnology Information	Molecular data and its cryptic and subtle patterns, biomedical and genomic information	The National Center for Biotechnology Information engaged, developed and coordinated access to a variety of databases, medical communities, basic and applied research in computational biology in informatics research and provided an absolute requirement for computerized databases and analysis tools	http://www.ncbi.nlm.nih.gov/
OMIM, Online Mendelian Inheritance in Man	Genes, genetic disorders	Online Mendelian Inheritance in Man, supported catalog of all known human genes and genetic phenotypes.	http://www.omim.org/
PDB, Protein Data Bank	Structural data of large biological molecules	Protein Data Bank presented a key resource in areas of structural biology, and biochemists.	http://www.pdb.org/pdb/home/home.do
PeptideAtlas, The Human PeptideAtlas	Different peptide and protein	The Human Peptide Atlas, establishment of a standard method for the submission of data to the Proteome Xchange consortium databases PRIDE, PeptideAtlas, and Tranche	http://www.proteinatlas.org/
UniProtKB, UniPro Knowledge	Protein annotation	The Universal Protein resource Knowledge, a central hub by combining the Swiss-Prot, TrEMBL and PIR-PSD databases provided accurate, consistent and rich annotation. To capturing the core data mandatory for each UniProtKB entry (mainly, the amino acid sequence, protein name or description, taxonomic data and citation information), as much annotation information as possible was added.	http://www.uniprot.org/

(1.7), Cryptococcosis (1.7), and measles (1.3). The results of exploited data revealed that PMP2 including 5.9 z, is the most powerful protein involved in neuritis disease (Table 2).

On the other hand, evaluation of information in proteomics databases combined with bioinformatics tools led to isolated collection of protein classes, which were associated with neuritis. Interestingly, this collection has been set base on Z score, too. Evidence displayed that PMP2, including 5.9 z, is the most powerful protein and, Aminoacyl tRNA synthetase complex-interacting multifunctional protein (AIMP1) is the protein (3.3z) with least power in neuritis disorders (Table 3).

Moreover, the interpretation of results revealed that leprosy, a neuroinfection disorder with high similarity with neuritis (30.6 z) relative to other diseases, involves IFNG protein (4.3 z), a secreted protein class, which is important in leprosy disease.

5. Discussion

Recent neuroinformatic and modeling of disease researches have used computational bioinformatics for the study of living organisms. These studies have highlighted the beginning of a quiet revolution in bioscience, system biology and reshuffling of disease considering protein classes (31). Interestingly, the combined evidence of validity and reliability between theoretical evaluations with conducted experimental observations is a merit of the bioinformatics methodology, which should be done prior to laboratory tests.

In this study, there was an emphasis on bioinformatics databases to present a hypothesis about the relationship between protein classes and human disease. Furthermore, the findings of the study were confirmed by interpretation of several databases.

The hypothesis, which was confirmed based on theoretical studies, suggested that one protein could be related to different diseases, and two different proteins could be the causative agent of one, while two related diseases could be associated with various protein classes and their protein classes could be different. These findings could indicate the complexity of this subject.

Evidences of this study suggested that causes related to human neuronal disease, are not only defective structural and functional proteins but also the association of various protein classes.

The evidence, based on the prognosis of this method, revealed that the proposed agent in protein –related prediction is not a single criterion such as Z score, MIFT score, or protein family, but rather a collection of these criteria are necessary. On the other hand, the results of differ-

Table 2. The association of PMP2 with disorders

Name	Z-Score	Classification
PMP2 (Peripheral myelin protein 2)	5.9	Predicted intracellular proteins
EDA (Ectodysplasin A)	4.2	Cytoskeleton related proteins, Disease related genes, Predicted intracellular proteins, Predicted membrane proteins
MLLT1 (Myeloid/lymphoid or mixed-lineage leukemia (trithorax homolog, Drosophila); translocated to, 1)	4.1	Cancer-related genes, Disease related genes, Predicted intracellular proteins
CD40LG (CD40 ligand)	3.6	Cancer-related genes, CD markers, Disease related genes, Predicted membrane proteins
MBP (Myelin basic protein)	3.6	Candidate cardiovascular disease genes, Disease related genes, Plasma proteins, Predicted intracellular proteins
CD4 (CD4 molecule)	3.5	CD markers, FDA approved drug targets, Predicted membrane proteins
MAG (Myelin associated glycoprotein)	3.3	Plasma proteins, Predicted intracellular proteins, Predicted membrane proteins
AIF1 (Allograft inflammatory factor 1)	3.3	Predicted intracellular proteins
LRP11 (Low density lipoprotein receptor-related protein 11)	3.3	Predicted membrane proteins, Predicted secreted proteins
AIMP1 (Aminoacyl tRNA synthetase complex-interacting multifunctional protein 1)	3.3	Disease related genes, Predicted intracellular proteins

Table 3. The Association of Neuritis Disorder With Protein Class

Name	Z-Score	Classification	Protein	Classification
Neuritis	5.9	Neuronal diseases	MPZ	Disease related genes, Predicted intracellular proteins, Predicted membrane proteins
Microsporidiosis	4.9	Rare diseases, Infectious diseases	METAP2	Enzymes, FDA approved drug targets, Plasma proteins
Pseudomyxoma peritonei	2.5	Rare diseases, Cancer diseases	MUC2	Predicted secreted proteins
Acute disseminated encephalomyelitis	2.3	Rare diseases, Neuronal diseases	MBP	Candidate cardiovascular disease genes, Disease related genes, Predicted intracellular proteins
Charcot-Marie-Tooth disease	2.2	Genetic diseases, Rare diseases, Fetal diseases, Metabolic diseases, Neuronal diseases, Ear diseases	GJB1	Disease related genes, Potential drug targets, Predicted membrane proteins, Transporters
Mumps	1.8	Rare diseases, Infectious diseases, Oral diseases	STAT2	Transcription factors
Demyelinating polyneuropathy	1.7	Rare diseases, Neuronal diseases	PMP22	Cancer-related genes, Disease related genes, Predicted intracellular proteins, Predicted membrane proteins
Cryptococcosis	1.7	Rare diseases, Infectious diseases	SELL	Cancer-related genes, Candidate cardiovascular disease genes, CD markers, Plasma proteins
Measles	1.3	Rare diseases, Infectious diseases, Skin diseases	CD46	Cancer-related genes, CD markers, Disease related genes, Plasma proteins, Predicted membrane proteins

Abbreviations: CD46, CD46 molecule, complement regulatory protein; GJB1, Gap Junction Protein, Beta 1, 32kDa; MBP, myelin basic protein; METAP2, Methionyl Aminopeptidase 2; MPZ, myelin protein zero; MUC2 Mucin 2, oligomeric mucus/Gel- forming; PMP22, peripheral myelin protein 22; SELL, selectin L; STAT2, signal Transducer and activator of transcription 2, 113kDa.

ent databases are confusing when considered separately. Thus, one needs to focus on collection of databases and development of comprehensive prediction, as previously described in the result section. Accordingly, a set of proteins and a panel of disorders were identified by the protein of each database. Overall, theoretical frameworks of all the protein fragments were interpreted. All mentioned evidences indicated the complexity of bioinformatics stud-

ies.

In this study, research was carried out based on a new theoretical approach exploited from bioinformatics tools. This approach could help researchers predict and design the study prior to investigation experimental studies. In addition, it is effective as a new method for confirmation of hypothesis of theoretical prediction and comprehensive studies based on in silico integrative in vitro studies.

5.1. Conclusions

The results of interpreted data from different proteomics databases suggested that two diseases that are related to each other, might involve different classes of proteins. Hypothesis of silico-based investigation with consolidated prediction prior to in vivo studies could increase the reliability of the study. Future researches should use bioinformatics for development of neuro-autoantigenic targets for the reshuffling and the etiology of different diseases.

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Footnote

Authors' Contribution: Samiie Pouragahi and Marjan Nassiri-Asl wrote the manuscript. Marjan Nassiri-Asl and Samiie Pouragahi designed the manuscript. Supervision of study was done by Marjan Nassiri-Asl, Mohammad Hossein Sanati and Mehdi Sadeghi.

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