MINING AND MAPPING OF PROTEIN-PROTEIN INTERACTION ASSOCIATED WITH DEMENTIA AND RELATED DISEASES

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MINING AND MAPPING OF PROTEIN-PROTEIN INTERACTION ASSOCIATED WITH DEMENTIA AND RELATED DISEASES

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Specially dedicated to my family members

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ABSTRACT

Dementia is a multi-causal syndrome caused by various types of neurodegenerative diseases. Symptoms of dementia include short memory, muscle contraction, poor judgement and it is the effect caused by gradual brain cell death. There is a need to understand the fundamental causes of this syndrome as dementia is historically well-documented with new cases increasing steadily every year yet it is still incurable. In this study, protein-protein interaction in diseases that have been shown to be associated with dementia such as Alzheimer's disease, Parkinson's disease, and Huntington's disease were mined and mapped. Results indicated that, nine proteins are found to be interconnected between four different diseases. Six out of nine proteins that belong to Fatal Familial Insomnia are also found in Creutzfeldt-Jakob disease. Although Alzheimer's disease has the most complex interaction map, only two proteins coexist in Frontotemporal Dementia and one protein in Creutzfeldt-Jakob disease. The interaction data of diabetes, hypertension and hypercholesterolemia were also mapped by adding into the map and seven proteins were found to be associated with Alzheimer's disease and two proteins with Parkinson's disease. The interconnector proteins were examined in gene co-expression database and some of the functional interactions were found to interact physically. Proteins that interact physically will initiate a reaction while functional interaction shows co-expression of some proteins on a specific location at a time. These results demonstrated how the combination of the protein-protein interaction data and functional interaction data obtained from gene coexpression database was useful to predict their possible relationship, in which the functional interactions are potentially interacting physically. This study allowed the prediction of protein-protein interaction through the combination of functional interaction and physical interaction as a methodology in proteomic studies.

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LIST OF ABBREVIATION

2D	-	2 Dimensional
3D	-	3 Dimensional
BioGRID	-	Biological General Repository for Interaction Datasets
BioPAX	-	Biological Pathway Exchange
BOND	-	Biomolecular Interaction Network Database
cDNA	-	complementary Deoxyribonucleic Acid
CoIP	-	Co-immunoprecipitation
CSV	-	Comma-separated values
CYGD	-	Comprehensive Yeast Genome Database
DNA	-	Deoxyribonucleic acid
et al.	-	and friends
GML	-	Geography Markup Language
GO	-	Gene Ontology
HAPPI	-	Human Annotated and Predicted Protein Interaction Database
HIV	-	Human Immunodeficiency Virus
HPID	-	Human Protein Interaction Database
HPRD	-	Human Protein Reference Database
HUPO	-	Human Proteome Organisation
I2D	-	Interolog Interaction Database
iHOP	-	Information Hyperlinked over Proteins
InterDom	-	Database of Interacting Domains
JNK	-	c-Jun N-terminal kinases
MeSH	-	Medical Subject Headings

MINT	-	Molecular Interaction Database
MIPS	-	Mammalian protein–protein interaction database
MMSE	-	Mini-Mental State Examination
NAViGaTOR	-	Network Analysis, Visualisation and Graphing Toronto
NCBI	-	National Center for Biotechnology Information
PDF	-	Portable Document Format
PNG	-	Portable Network Graphics
PPI	-	Protein-protein interaction
PSI	-	Proteomics Standards Initiative
PSI-MI	-	Proteomics Standards Initiative- Molecular Interaction
RDF	-	Resource Description Framework
RNAi	-	Ribonucleic acid interference
SAGE	-	Serial Analysis of Gene Expression
SIF	-	Simple Interaction Format
SNP	-	Single Nucleotide Polymorphisms
SVG	-	Scalable Vector Graphics
TAP-MS	-	Tandem affinity purification coupled to mass spectrometry
TIFF	-	Tagged Image File Format
UniProt	-	Universal Protein Resource
VRML	-	Virtual Reality Modeling Language
XGMML	-	Extensible Graph Markup and Modeling Language
XML	-	Extensible Markup Language

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CHAPTER 1

INTRODUCTION

1.1 Background of study

Dementia, which mostly affects elderly people, is not a disease, but a complex multi-causal syndrome caused by a variety of mechanisms (Hauw and Duyckaerts, 2002, Korczyn, 2009). Patients who are diagnosed with dementia may face difficulties in his daily life as he will lose the ability to make judgments, calculation, comprehension and learning. In addition, dementia sufferers have poor memory with difficulties in thinking, speaking, and recognising direction (World Health Organisation, 1992). Early diagnosis and treatment may reduce the affliction caused by dementia, but this syndrome is not often diagnosed in the early stage (Boustani *et al.*, 2003). The number of patients that have developed dementia is gradually increasing and is expected to double every 20 years, causing great economic loss in human society (Korczyn, 2009). Therefore, there is a need to understand the aetiology of dementia as new cases are steadily increasing every year due to extended life expectancy and yet it is still incurable.

To understand how dementia occurs, researchers have tried to look into the molecular level of the disease, which are protein-protein interaction. According to Kocatas and his co-workers (2003), protein-protein interaction are crucial in understanding the biological processes and disease mechanisms in living organisms. Suzuki (2006) also suggested that the protein-protein interaction network in various types of brain cells provide useful knowledge in recognizing the complication and the

1.3 Objectives

1. To mine all the proteins related to various types of diseases in dementia.
2. To map all the protein-protein interaction for different diseases in dementia and its associated risk factors and study their relationship.
3. To find new interactions between dementia and its associated diseases.

1.4 Scope of study

In this research, the focus was on the diseases associated with dementia. The proteins involved in the diseases were mined from protein-protein interaction databases which store the physical interactions generated from laboratory experiments and excluding all the predicted interactions. The results were then mapped using a suitable visualisation tool. One visualisation tool was chosen to view and the analysis of the protein-protein interaction and a prediction on protein-protein interaction were performed by comparing the functional interactions obtained from gene co-expression laboratory data with the data from physical interactions.

1.5 Significance of study

From this research, creating one protein-protein interaction network map connecting various dementia associated diseases would provide useful information regarding the relationship among them. It can acts as a starting point for us to further examine the interconnected proteins in these diseases. An example would be the determination of novel biomarkers and single treatment for multiple interconnected diseases. Shared lethal protein or pathogenic mechanism may also be discovered through the mapping of interactions as well as predicting new protein-protein interaction which not yet been discovered through laboratory experiments.

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