Analysis of protein interaction networks in neurodegenerative disorders

Vachiranee Limviphuvadh[1]
limvip@kuicr.kyoto-u.ac.jp

Seigo Tanaka[2]
seigo@scl.kyoto-u.ac.jp

Susumu Goto[1]
goto@kuicr.kyoto-u.ac.jp

Kunihiro Ueda[2]
ueda@scl.kyoto-u.ac.jp

Minoru Kanehisa[1]
kanehisa@kuicr.kyoto-u.ac.jp

[1] Laboratory of Bioknowledge Systems, Bioinformatics Center,
[2] Laboratory of Molecular Clinical Chemistry, Division of Bioorganic Chemistry,
Institute for Chemical Research, Kyoto Univerisity, Uji, Kyoto 611-0011, Japan

Keywords: neurodegenerative disorders, protein-protein interaction networks

1 Introduction

Neurodegenerative disorders (NDDs) are progressive and fatal disorders whose neurobiological bases are not well understood. A unifying and common feature of neurodegenerative disorders is the abnormal accumulation and processing of mutant or damaged intra- and extracellular proteins. The molecular steps leading to the specific neuropathology of each disease are unknown and are still under intensive investigation. Finding proteins that interact with causative genes is an important step for elucidating (1) the normal function of the causative genes and (2) the possible role of the interacting proteins in the disease, consequently increasing our understanding of the pathogenesis of NDDs. The objective of our research is to understand the pathology of the diseases and any common molecular pathogenic mechanisms in terms of the protein-protein interaction network in NDDs.

We have already constructed a knowledge-base which provides information about protein-protein interactions in six NDDs: Alzheimer's disease (AD), Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Dentatorubral-pallidoluysian atrophy (DRPLA) and Prion disease. This information was collected through a critical reading of the published literature.

In addition to the data we accumulated, this research combined other comprehensive protein-protein interaction data and gene expression data in order to find proteins that are linked to causative genes in these six NDDs.

2 Data and Method

Currently, our knowledge-base contains 207 proteins and 263 interactions which were confirmed to be expressed in the brain. From this data, we found 17 proteins that are shared by at least two NDDs, but we could not find any common proteins that were related to all the diseases. From our knowledge-base, we extracted the proteins that interact with ten known causative genes in the six NDDs, which include the amyloid precursor protein, presenilin 1, presenilin 2, apolipoprotein E, synuclein-α, parkin, superoxide dismutase 1, huntingtin, atophin-1 and prion. We call these proteins first-step neighbors from the causative genes. Next, we used human protein-protein interaction data from Human Protein Reference Database (HPRD) version 1.0 [1]. This database contains proteins that interact with OMIM proteins, accumulated by manual annotation from the literature. At present, the database includes 8,805 proteins and 19,319 interactions. We collected proteins interacting with the first-step neighbors from HPRD, calling them second-step neighbors. Then, brain-specific proteins were extracted as the final second-step neighbors by limiting the second-step neighbors to those that are highly expressed only in brain (618 genes) from the Human Gene Expression Index Database (HugeIndex) [2], a public repository for gene expression data on

normal human tissues using high-density oligonucleotide arrays. We used the first-step neighbors and the final second-step neighbors to create a protein-protein interaction network.

3 Results and Discussion

From our knowledge-base, we yielded 179 proteins and 217 interactions as the first-step neighbors. We collected 1,296 proteins and 1,962 interactions as the second-step neighbors from HPRD. By limiting to brain-specific proteins based on HugeIndex, we obtained 203 proteins and 255 interactions as the final second-step neighbors. The combination of first-step neighbors and final second-step neighbors resulted in 282 proteins and 435 interactions. The distribution of the functions of the proteins involved in the protein-protein interaction network is shown Figure 1. We found that the biological process categories of "Cellular communication and signal transduction," "Cellular organization," "Protein synthesis, processing and protein fate" and "Apoptosis" were more abundant when compared with all the human proteins in HPRD, whereas the categories of "Immunity," "Storage transport," "Energy metabolism" and "Nucleic acid synthesis and processing" were lower. It has already been argued that apoptosis and protein synthesis, processing and protein fate are, at least, common mechanisms. Our results support this argument. We are now investigating the functions of proteins involved in the above categories in the NDDs.

From this interaction network, we searched a path that starts from one causative gene and ends with another causative gene in the NDDs. As a result, we found 70 proteins involved in this path. Fifty-four percent of these were categorized under cellular communication and signal transduction, and most of these proteins were related to the MAPK signaling pathway and the Wnt signaling pathway. Finding the relationship between these pathways in the NDDs is an area of research for future work.

Biological process	All proteins in the network	All proteins in HPRD
Apoptosis	9 (3.2%)	35 (0.4%)
Cellular communication and signal transduction	110 (39.0%)	2,446 (27.8%)
Cellular organization	26 (9.2%)	535 (6.1%)
Energy and metabolism	19 (6.7%)	1,059 (12.0%)
Immunity	6 (2.1%)	391 (4.4%)
Nucleic acid synthesis and processing	32 (11.3%)	1,512 (17.2%)
Protein sysnthesis, processing and protein fate	37 (13.1%)	836 (9.5%)
Storage and transport	12 (4.3%)	646 (7.3%)
Cell cycle control protein	0 (0.0%)	3 (0.0%)
DNA repair protein	0 (0.0%)	1 (0.0%)
Unclassified	31 (11.0%)	1,341 (15.2%)
Total	282	8,805

Figure1. Distribution of protein functions in the network.
(The functional category is based on the biological process in HPRD.)

Acknowledgements

This work was supported by grants from the Ministry of Education, Culture, Sports, Science and Technology, the Japan Society for the Promotion of Science, and the Japan Science and Technology Corporation. The computational resource was provided by the Bioinformatics Center, Institute for Chemical Research, Kyoto University.

References

[1] Peri S. *et.al.*, Development of human protein reference database as an initial platform for approaching systems biology in humans, *Genome Res*., 13(10): 2363-71, 2003.

[2] Hsiao LL *et.al.*, A compendium of gene expression in normal human tissues, *Physiol Genomics*., 7(2):97-104, 2001.