Vol 5 (2), July 2014, 01-05

The Protein-Protein Interaction of Parkinson's disease Associated Pin-1 Gene by using STRING's Network.

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ABSTRACT

Parkinson's disease is the next frequent neurodegenerative disorder after Alzheimer's, caused primarily by the loss of dopaminergic neurons of the Substantia Nigra. Mutations in the Putative-induced Kinase - a mitochondrial Serine/Threonine-protein Kinase encoded by the PINK1 gene have been found in families with recessive early-onset Parkinson's disease.

The present study represents the protein-protein interaction of PINK1 gene which is mutated in some forms of Parkinson's disease by using advanced Bioinformatics tools such as STRING's Network and BIOGRID data base.

In conclusion, Protein-protein interaction networks are an important ingredient for the system-level understanding of cellular processes such, networks can be used for assessing functional genomics data, providing an intuitive platform for annotating evolutionary properties of proteins and their structural and functional features.

Keywords: *PINK-1, Parkinson's disease, Protein-protein interaction, STRING's network*

INTRODUCTION

Parkinson's disease cause progressive movement disorder, illustrated by loss of dopaminergic neurons in the region of Substantia Nigra and neuronal intracellular Lewy body inclusions. It is characterized clinically by tremor, rigidity, postural instability and bradykinesia (Paisán-Ruíz *et al.*, 2004; Shen, 2004).

The disease is diagnose by achromasia of the substantia nigra pars compacta and the presence of lewy bodies in brain stem while currently motor disability has been alleviated. The diagnosis of Parkinson's disease is made only on the basis of clinical criteria. The standardized test for the diagnosis of the disease remains the neuropathological examination, since no biological marker has yet been identify to confirm the diagnosis (Toda, 2007; Vila and Przedborski, 2004; Anthony and Lozano, 1998).

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Currently, protein-protein interactions are annotated at a choice of levels of detail in online resources, ranging from raw to highly formalized pathway databases. For several applications, a large-scale analysis of all the available interaction data is desirable, including computational predictions etc. (Berman *et al.*, 2000; Bork *et al.*, 2004).

The database STRING is a precomputed global resource for the exploration and analysis of these associations. It is essential to assess and compare the significance of individual predictions as these evidences differ not only conceptually but also the predicted interactions are very vast. The graphical picture of the network is conditional with respect to protein interactions provides an advanced view of functional linkages that facilitate the analysis of modularity in biological processes. The database accurately predicts functional interactions up to 80% for more than half of the

genes (Kolatkar et al., 1998).

FASTA is another frequently used sequence match search tool uses for fast local alignment searching. BIOGRID - the Biological General Repository for Interaction Datasets (http// thebiogrid.org) provides genetic / protein interactions that are collected from the primary biomedical literature for all major model organism species. These associated data sets permit the construction of interaction networks from a variety of data sources used to explain biological processes interpreting and predicted biological functions of these proteins. (Gerstein, 2000; Huttenhower *et al.*, 2009).

In the present study the affiliation of PINK1 gene with Parkinson's disease, their associated functional partners and the protein-protein interactions were analyzed by using advanced bioinformatics tools such as, STRING network and BIOGRID database.

MATERIALS AND METHODS

Computational analysis made possible in-depth knowledge of PINK1 gene which is associated in the progression of Parkinson's disease by using Neuroinformatics tools like Gene Bank, STRING's Network, UniProt Kb/SwissProt Database, and BIOGRID Data Base.

The Uniprot/ Swiss-Prot database that provides the protein knowledgebase includes complete and reference proteome sets. STRING 8.3 (http://string-db.org/) was used to explore the biological associations of knowledge base differentially expressed protein.

RESULTS

The present study represents the protein-protein interaction of PINK1 gene which is mutated in some forms of Parkinson's disease by using advanced Bioinformatics tools such as STRING's Network and BIOGRID data base.

TABLE#1 depicted the basic information about PINK1 which was available on gene bank & gene card suggested that it is a protein coding gene having a protein name "putative induce kinase1" it is refer to a family of serine/ threonine kinase 1 predicted for its various phosphorylation behavior. The molecular weight of PINK1 gene is 62,769 Da. Due to defects in functions of PINK1 gene leads the down level of dopaminergic neuron which is the leading factor in the progression of Parkinson's disease. FIGURE-1 represent the chromosomal location of pink 1 gene has been actuated by the gene card figure out that it is present on chromosome 1 at position 36.12.

String network predict the functional partners of pink1 gene PARK2, HTRA2, TRAP1, CDC37, ATP13A2, RICTOR, DUSP6, ODC1. (FIGURE-2 a, b, c). The edges represent the predicted functional associations. An edge may be drawn with up to 7 differently colored lines - these lines represent the existence of the seven types of evidence used in predicting the associations. A red line indicates the presence of fusion evidence of PARK2, HTRA2, PARK7 with PINK1 a green line - neighborhood evidence and a blue line -co occurrence evidence with TRAP2, DUSP6, ODC37, ATP13A2, HTRA2, PARK2, PARK7, FABP4, RICTOR, a purple line indicates experimental evidence with TRAP1& CDC37, a yellow line with FBP4 having text mining evidence; a light blue line - database evidence Associated with ATP13A2, PARK2, PARK7 a black line - co expression evidence predicted between TRAP1 &CDC37.

The functions of the predicted genes are given below:

PARK2: Parkinson disease (autosomal recessive, juvenile) 2, parkin; Functions within a multiprotein E3 ubiquitin ligase complex, catalyzing the covalent attachment of ubiquitin moieties onto substrate proteins, include

SYT11, CCNE1, GPR37 etc., may play a more general role in the ubiquitin proteosomal pathway by participating in the removal and/or detoxification of abnormally folded or damaged protein. Loss of this ubiquitin ligase activity appears to be the mechanism underlying pathogenesis of PARK2.

HTRA2: serine peptidase 2; Serine protease that shows proteolytic activity against a non-specific substrate beta-casein. Promotes or induces cell death either by direct binding to and inhibition of BIRC proteins (also called inhibitor of apoptosis proteins, IAPs), leading to an increase in caspase activity, or by a BIRC inhibition-independent, caspase-independent and serine protease activity-dependent mechanism.

DUSP6: dual specificity phosphatase 6; Inactivates MAP kinases. Has a specificity for the ERK fatty acid binding protein 4, adipocyte; Lipid transport protein in adipocytes. It binds with both long chain fatty acids and retinoic acid and delivers to their cognate receptors in the nucleus.

Table 1: Classification and Function of Pink 1 Gene

GENE	**PINK1**
Organism	Homosapiens
Gene type	Protein coding
Family name	Protein kinase » Ser/Thr protein kinase entry whose protein existence is based on evidence at protein level
Protein	Serine/threonine-protein kinase PINK1, Mitochondrial protein.
Alt. Names/Synonyms	BRPK; FLJ27236; PARK6; PINK1; protein kinase BRPK; PTEN induced putative kinase 1; Serine/threonine-protein kinase PINK1.
Locus	1p36.12
Molecular Weight	62,769 Da
Basal Isoelectric Point	9.43 Predict pI for various phosphorylation states
Tissue specificity	Highly expressed in heart, skeletal muscle and testis, and at lower levels in brain, placenta, liver, kidney, pancreas, prostate, ovary and small intestine. Present in the embryonic testis from an early stage of development.
Cellular Component	Mitochondrial outer and inner membrane cytoskeleton; cytosol; nucleus; chromatin.
Molecular function	1. Protein serine/threonine kinase activity; 2. Protein binding; 3. Ubiquitin protein ligase binding; 4. Magnesium ion binding; 5. Kinase activity; /ATP binding.
Biological process	1. Cell death; 2. Positive regulation of dopamine secretion, peptidyl-serine phosphorylation. 3. Positive regulation of synaptic transmission, 4. Mitochondrion degradation; response to stress, regulation of protein complex assembly. 5. Negative regulation of neuron apoptosis, protein amino acid phosphorylation.
Catalytic activity	ATP+ a protein = ADP+ a phosphoprotein
Cofactor	Magnesium

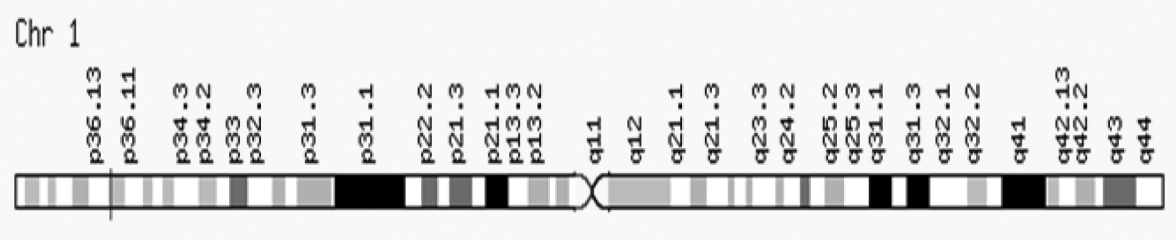

Figure 1. Chromosomal Location of PINK1 Gene.

Figure 2a, b, c. String Network Predict Functional Partners Of Pink 1 Gene.

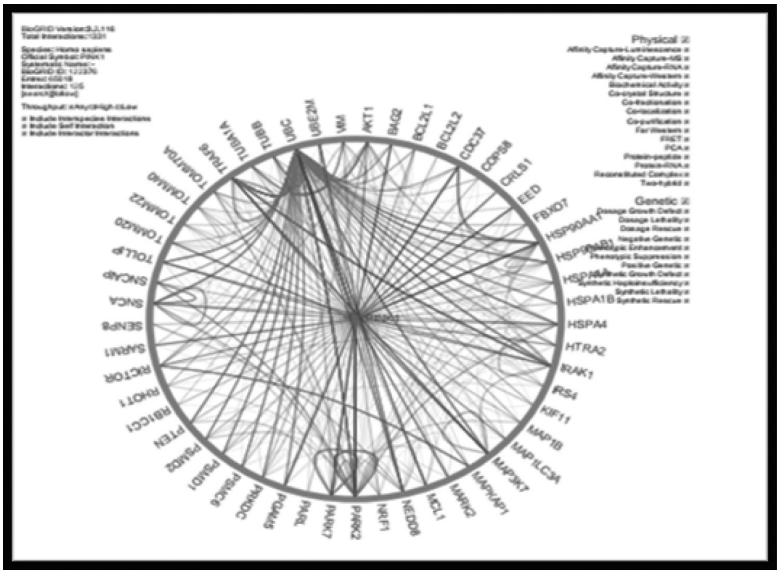

Figure 3. PINK1 Interaction with Different Proteins by BioGrid.

TRAP1: TNF receptor-associated protein 1; Chaperone that expresses an ATPase activity.

CDC37: microRNA 1181; Co-chaperone that binds to numerous kinases and promotes their interaction with the Hsp90 complex, resulting in stabilization and promotion of their activity.

PARK7: Parkinson disease (autosomal recessive, early onset) 7; Acts as a positive regulator of androgen receptor-dependent transcription, may function as a redox-sensitive chaperone and as a sensor for oxidative stress. Prevents aggregation of SNCA. Protects neurons against oxidative stress and cell death plays a role in fertilization. **ODC1:** ornithine decarboxylase 1.

RICTOR: RICTOR independent companion of MTOR, which regulates cell growth and survival in response to hormonal signals. MTORC2 plays a critical role in AKT1 'Ser-473' phosphorylation, which may facilitate the phosphorylation.

FIGURE-3 depicts BIOGRID database that helps in determination of Pink1 partners

under the influence of environmental and genetic factors such as UBC, PAG2, CDC37, CRLS1,EED, HSP90AA1, PARK2, PARK7, SRM1.

DISCUSSION

The cellular behaviour is dictated by a complex global network of protein interactions, which are modified at the level of gene expression, messenger RNA (mRNA) stability, translation rate, degradation, localization and post-translational modifications. The inter connectivity of the physical interaction network is reflected by a massively dense network of genetic interactions.

The present study comprises on the determination of the functional protein partners of protein Parkin or PINK1 gene, which is mutated in some forms of familial Parkinson's disease, is recruited from the cytoplasm to damaged mitochondria and that this leads to the breakdown of the mitochondria by processes acting within the cell, by using advanced bioinformatics tools such as STRING's NETWORK and BIOGRID database.

A variety of mutations in the PINK1 and Parkin genes cause early-onset Parkinson's disease in humans. The mitochondrial membrane protein PINK1 is also mutated in some forms of familial Parkinson's disease. PINK1 gene - the Putative-Induced Kinase - mitochondrial Serine/Threonine-Protein Kinase mutations have been found in families with recessive early-onset Parkinson's disease. PINK1 might accumulate in damaged mitochondria because of increased synthesis and/or reduced degradation of the protein. Excessive PINK1 accumulation on mitochondrial membranes is therefore sufficient to recruit Parkin and activate mitochondrial autophagy, even in the absence of membrane depolarization.

CONCLUSION

Neuroinformatics approach in the current study expressed unique possibilities to enhance understanding towards the biological function of the particular gene like PINK1 gene which is associated with the progression of Parkinson's disease. Protein-protein interaction networks are an important ingredient for the system-level understanding of cellular processes. Such networks can be used for filtering and assessing functional genomics data and for providing an intuitive platform for annotating structural, functional and evolutionary properties of proteins.

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