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ORIGINAL ARTICLE

DRD2 Gene: Insilico Approach for Functional Protein Partners and Regulatory Pathways Analysis

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ABSTRACT

Bioinformatics methodologies have made possible to profile the global composition of tissue or organelle at specific time point or under particular developmental or disease state. Extensive research into the genomics of neuropsychiatric diseases such as schizophrenia - a chronic brain disorder that may develop from a combination of multiple factors and affects approximately 1% people worldwide has revealed the importance of DRD2 gene in the development of disease. The study depicts the computational analysis of DRD2 gene exploring molecular networks of interacting targets by STRING's database, KEGG and Reactome pathways and BioGrid databases- current bioinformatics tools that may provide insights into the biological processes underlying schizophrenia.

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Introduction

Several susceptibility genes that influence brain structure/function are hypothesized to be involved in schizophrenia making it difficult to determined (1), as a consequence the disease etiology is remains obscure. However, it is hypothesized that the dysregulation of dopaminergic neurotransmission has become the main factor involved in the pathogenesis of schizophrenia (2-5).

Both classical/second generation antipsychotic drugs act through dopamine receptors (d1-d5) either by increasing intracellular cAMP or by inhibiting intracellular cAMP on stimulation. (4, 6). The association between increased DRD2-binding density and schizophrenia has been reported suggesting that DRD2 is critically involved in the expression of schizophrenia and becomes a risk gene for the neuropsychiatric disorders (3).

The most extensively used protein-protein interaction (PPI) databases includes the STRING-Search Tool for the Retrieval of Interacting Genes/Proteins, used to predicted protein-protein interactions, DIP - Database of Interacting Proteins, and Reactome that provide pathways related PPI information. (7).

In the present study the affiliation of DRD2 gene with Schizophrenia, their associated functional partners and the protein-protein interactions were analyzed by using STRING network and KEGG & REACTOME pathways.

Materials and Method

Computational analysis made in-depth knowledge of DRD2 gene which is associated in the progression of Schizophrenia by using bioinformatics tools like Gene Bank, STRING's Network, REACTOME Pathway, KEGG, Uniprot / SwissProt Database, Gene Cards, and BIOGRID Database.

The Uniprot/ Swiss-prot database that provides the protein knowledge base includes complete and reference proteome sets. KEGG Pathway is a collection of manually drawn pathway maps. REACTOME is an open-source,

curetted and peer reviewed pathway database. STRING 10 was used to explore the biological associations of knowledge base differentially expressed protein.

Results

In this study the DRD2 gene was subjected to the advanced Bioinformatics tools and software such as STRING network, for identification of the predicted protein-protein interactions (PPI) of DRD2 gene, KEGG-pathway to understand the dopaminergic synapse system as well as the disease related to dopaminergic synapse, and REACTOME to identify neural function of dopamine i.e. signal transduction.

TABLE#1 depicted the basic information about DRD2 which was available on gene bank, gene cards and OMIM suggested that it is a protein coding gene having a protein name “Dopamine receptor D2”. The molecular weight of DRD2 gene is 50619 Da.

FIGURE-1 represents the chromosomal location of DRD2 gene has been actuated by the gene card figure out that it is present on chromosome 11 at position 23.

2. FIGURE-2 (a, b, c) represents the String network to predicts the functional partners of DRD2 gene SLC6A3, PDYN, SSTR5, SST, CNR1, POMC, GNAI3, KCNJ6, PENK, NPY

FIGURE-3 depicts the KEGG Pathway of DRD2. Dopamine is a significant neurotransmitter present in the brain critically involved in modulation of various biological functions. FIGURE-4 represents the Signal transduction pathway by using REACTOME software while FIGURE-5 shows nicotinic pathway of DRD2.

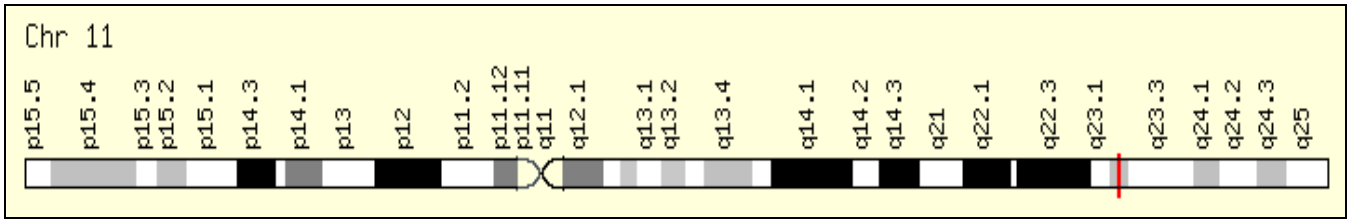


Figure 1. Chromosomal Location of DRD2 Gene

Figure 2a, b, c. String Network Predicted Functional Partners of DRD2 Gene

A .Evidence View **B. Confidence View** **C. Action View**

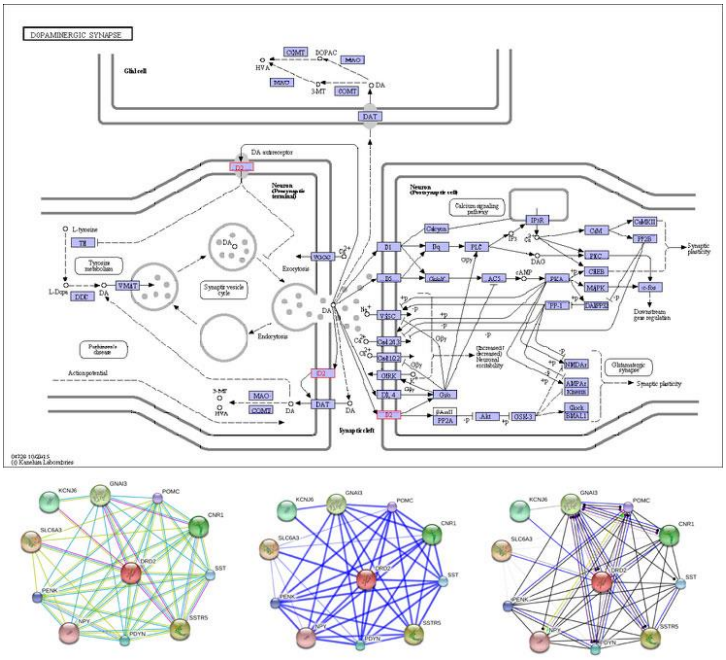


Table 1: Classification and Function of DRD2 Gene

Gene	DRD2
Organism	Homosapiens
Gene type	Protein coding
Cytogenetic location	11q23.2
Size	443 amino acids
Molecular weight	50619 Da
Lineage	Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorrhini; Catarrhini; Hominidae; Homo
Molecular Function	• Dopamine binding • Dopamine neurotransmitter receptor activity, coupled via Gi/Go • Drug binding • Identical protein binding • Potassium channel regulator activity
Biological process	• activation of protein kinase activity • adenohypophysis development adenylate cyclase-inhibiting dopamine receptor signaling pathway • arachidonic acid secretion • associative learning auditory behavior axonogenesis • branching morphogenesis of a nerve • cellular calcium ion homeostasis • cerebral cortex GABAergic interneuron migration • circadian regulation of gene expression dopamine metabolic process feeding behavior • G-protein coupled receptor internalization • intracellular signal transduction • locomotory behavior • long-term memory • negative regulation of adenylate cyclase activity,blood pressure,cell migration, cell proliferation, circadian sleep/wake cycle, sleep, cytosolic calcium ion concentration, dopamine receptor signaling pathway, dopamine secretion, innate immune response, insulin secretion' protein kinase B signaling, protein secretion, synaptic transmission, glutamatergic, voltage-gated calcium channel activity neurological system process involved in regulation of systemic arterial blood pressure • neuron-neuron synaptic transmission • orbitofrontal cortex development • peristalsis • phosphatidylinositol metabolic process • phospholipase C-activating dopamine receptor signaling pathway • pigmentation • positive regulation of cytokinesis, cytosolic calcium ion concentration involved in phospholipase C-activating G-protein coupled signaling pathway, dopamine uptake involved in synaptic transmission, ERK1 and ERK2 cascade, glial cell-derived neurotrophic factor secretion, G-protein coupled receptor protein signaling pathway, growth hormone secretion, long-term synaptic potentiation, multicellular organism growth, neuroblast proliferation, receptor internalization, renal sodium excretion, transcription from RNA polymerase II promoter, urine volume • prepulse inhibition • protein localization • regulation of cAMP metabolic process, dopamine secretion, dopamine uptake involved in synaptic transmission, heart rate, long-term neuronal synaptic plasticity, phosphoprotein phosphatase activity, potassium ion transport, sodium ion transport, synapse structural plasticity, synaptic transmission, GABAergic, sequestered calcium ion into cytosol • response to amphetamine, axon injury, cocaine, ethanol, drug, histamine, hypoxia, inactivity, iron ion, light stimulus, morphine, nicotine, toxic substance • sensory perception of smell • striatum development • synapse assembly , synaptic transmission, dopaminergic • temperature homeostasis • visual learning and signaling pathway

Figure 3. KEGG Pathway of DRD2
http://www.genome.jp/kegg-bin/show_pathway?hsa04728
Dopaminergic synapse - Homo sapiens (human)
Figure 4. Signal Transduction Pathway
http://www.reactome.org/PathwayBrowser/#/R-HSA-162582&FLG=P14416

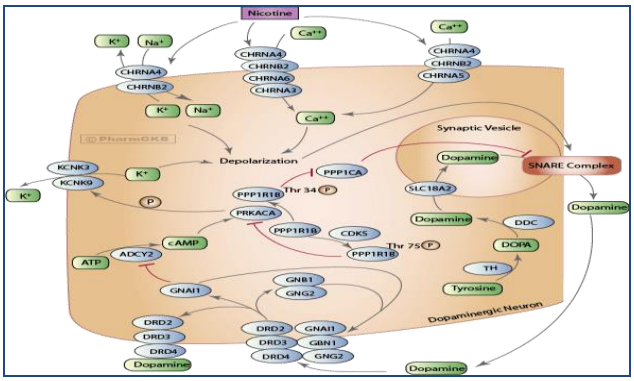
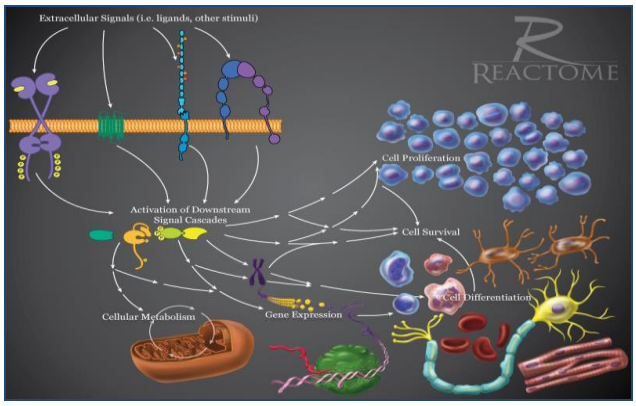


Figure-5 Nicotine Pathway of DRD2



https://www.pharmgkb.org/pathway/PA162355621

Discussion

Computational analysis aids in the prediction of individual gene function, cellular interaction networks and their contribution in regulation of cellular physiology. To understand the networks involved in human disease, bioinformatics play a significant role in the development and/or increase in availability of human protein interaction data that has been focused the understanding networks encoded in different species (8).

By using biocomputing techniques we extract out the informative data about DRD2 gene. Genomic location, function, catalytic activity, sub cellular location, Iso-electric point and family belonging of DRD2 gene have been accumulated by gene bank/gene card data analysis. The present study comprises on the computational bioinformatics analysis of DRD2 gene which is strongly associated with schizophrenia and other neuropsychiatric disorders.

The String network is used to predict the functional partners of DRD2 gene that includes; SLC6A3, PDYN, SSTR5, SST, CNR1, POMC, GNAI3, KCNJ6, PENK, NPY(Figure 2). In order to predict the associations, existence of the four (marked by 4 different colored lines) types of evidence were used. A purple line designates experimental evidence with KCNJ6, SLC6A3, SSTR5 and GNAI3. A light blue line shows database evidence associated with KCNJ6. A yellow line depicts association with SLC6A3, PDYN, SSTR5, SST, CNR1, POMC, GNAI3, KCNJ6, PENK and NPY. A purple-blue line with SSTR5 having homology evidence.

The functions of the predicted genes are given below:

- ✓ SLC6A3: solute carrier family 6 – a dopamine transporter, it functions in the presynaptic terminals to terminate the action of dopamine via sodium-dependent reuptake.
- ✓ PDYN: prodynorphin (Leu-enkephalins) takes part in many physiologic functions, compete with and imitate the effects of opiate drugs including pain perception and stress.
- ✓ SSTR5: somatostatin receptor 5; Receptor for somatostatin 28 and to a lesser extent for somatostatin-14. G proteins mediate the action of this receptor.
- ✓ SST: somatostatin; Somatostatin prevents the discharge of somatotropin.
- ✓ CNR1: cannabinoid receptor 1 (brain), these receptors are members of the G-protein family, that cease the activity of adenylate cyclase in a dose-dependent, stereoslective and pertussis toxin-sensitive manner.
- ✓ POMC: proopiomelanocortin; ACTH activates the adrenal glands to release cortisol.
- ✓ GNAI3: G proteins are concerned as transmembrane modulators/transducers in several signaling systems. They may involve in the process of cell division.
- ✓ KCNJ6: G-protein-coupled potassium channel receptors involved in the regulation of insulin secretion by glucose and/or neurotransmitters.

- ✓ PENK: proenkephalin (Met/Leu-enkephalins) involved in a number of physiologic functions and participate with the effects of opiate drugs including pain perception and stress.
- ✓ NPY: Neuropeptide Y is implicated in the regulation of feeding and in the release of gonadotrophin-release hormone.

The KEGG Pathway of DRD2 depicted in Figure 3. Dopamine - a neurotransmitter that modulates a number of physiological functions including reward pathway, learning and memory etc., interacts with 5 receptor subtypes designated as d1-d5, as it released from presynaptic axonal terminals. The receptors D1/D5 respond through adenylyl cyclase and cAMP production, while D2-D4 mediates its response via inhibition of adenylyl cyclase and cAMP production. Intracellular Ca2+ levels/dependent signaling systems are regulated by D1Rs and D2Rs. The synthesis and release of DA is regulated by D2Rs localized presynaptically as the main auto receptor of the dopaminergic system.

Figure 4 represents the Signal transduction pathway using REACTOME software. Signal transduction process the extracellular signals through the transmembrane receptors. Binding of ligands (both internal and external stimuli) stimulates these receptors resulting to transmit the signal via signaling cascades control different cellular processes.

The Nicotinic pathway of DRD2 depicted in Figure 5 shows that n-acetylcholine receptors in the brain is specific for the nicotine, while its binding with the DRD2 receptor results in depolarization associated with the release of dopamine via SNARE complex in the cell. This release activates Gi alpha to inhibit dopamine via feedback inhibition. A bi-functional signal transduction molecule (PPP1R1B) causes inhibition of either serine/threonine kinase/phosphatase; however its phosphorylation could further inhibit the dopamine release (9).

Conclusion

As Human network data remains elusive may be due to the biological, technological and/or algorithmic challenges still faced regarding molecular networks of a particular disease. In the present study, this Insilico approach provides more in depth perceptive about the functional significance of DRD2 gene and its association in the pathophysiology of Schizophrenia. The current accessibility of molecular interaction networks in humans has revolutionized the significance for both proteins and their interactive partners. However, utilizing advancement in these networks updates our analysis about disease progression, diagnosis, and treatment.

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