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DRUG TARGET PREDICTION BASED ON HUMAN HIV-1 PROTEIN-PROTEIN NETWORK

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ABSTRACT

Up to now, there have no fundamental methods to treat HIV-1(Human Immunodeficiency Virus type1). We constructed a network by the primary gene and protein of hiv-1 and then the corresponding dominating set. Considering the Network properties: degree, betweenness centrality, Characteristic path length and Clustering coefficient etc. This paper analyzes those two networks' properties, so as to find out the cdkn2a is a potential drug targets.

Keywords: *Proten-Proten Network,Betweenness Centrality,Dominate Set*

1. INTRODUCTION

The incidence of acquired immunodeficiency syndrome (AIDS) has increased over the past few decades. Up to now, nearly 34 million people have been suffered from human immunodeficiency virus-1 (HIV-1) infection, and an estimated 2.7 million people were newly infected with the virus in 2010 (http://www.who.int/features/factfiles/hiv/facts/en/index3.html). But, the natural course of HIV-1 infection and the susceptibility to infection after exposure are highly heterogeneous among individuals [1] .

In the past decades, the effective preventive measures against HIV are population screening and prevention of HIV transmission. Such as male circumcision, vaginal microbicide gel, pre-exposure prophylaxis(PrEP), and vaccination, etc. However, no one of those methods could effectively treat AIDS[2].

The houman body is made up of proteins, which is regulated by gene. Those genes and proteins composite a network.

A network is a set of nodes, and edges between the nodes. Networks enable studying the properties of complex systems that emerge from interactions among individual parts. Hence, networks have been used to model and analyze many real-world phenomena in numerous domains. Examples include social, technological, transportation, information, financial,ecological, chemical, and biological systems. We focus on protein-protein interaction networks, with the goal of understanding complex protein functioning by studying protein as inter-connected systems rather than as a collection of individual constituents. Nodes in these networks represent biomolecules, such as genes, proteins, and edges connecting the nodes indicate functional, physical, or chemical interactions between the

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corresponding biomolecules.

2. DATA AND METHODS

2.1. Data capture

HIV genes (HIV) are human genes known to interact with genes of the HIV virus that are available from HIV-1 Human Protein Interaction Database(http://www.ncbi.nlm.nih.gov/RefSeq/HIVInteractions/) .

HIV proteins and its regulatory genes are shown in Fig 1. We obtained the data from one of the interactome databases-Biogrid, Intact or DIP, and we excluded the dataset focused on proteins of a specific biological function..

Use the data of table 1 to build network shown in Fig 2 A.

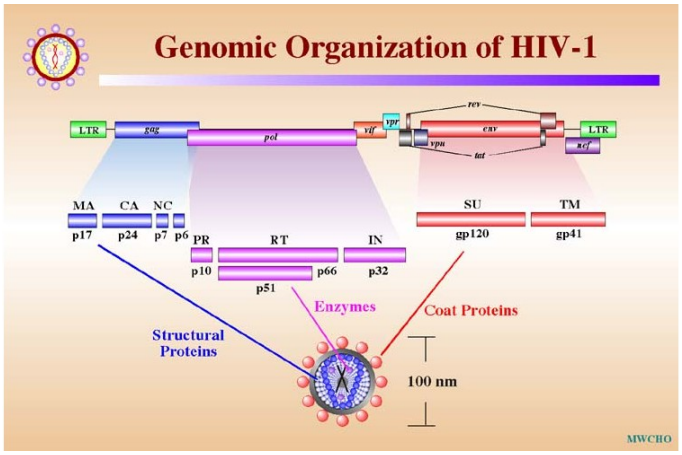

Figure 1 Genomic Organization Of HIV-1(The Picture Come Form Internet)

Table 1 Gene And Protein Of HIV-1

gene	Function	Position	Hiv-1
gag	precursor		P55
	Matrix protein	Virus particles	P17
	shell	Virus particles: nucleus	P24
	nuclear shell	Virus particles:DNA	P9
		Virus particles	P6
pol	protein	Virus particles	P10
	reverse transcriptase		P66
	reverse transcriptase		P51
env	Integrase precursor		P34 Gp160
	Envelope surface glycoprotein	Virus particles:surface	Gp120
		transmembrane protein	Gp41
Vif		infection cell	P23
tat	transcription	infection cell	P14
Rev	Control RNA cutting and running		P19
Vpu	Control CD4-env interaction	infection cell:surface	P15
Nef	Adjust CD4 express	infection cell:membrane	P27

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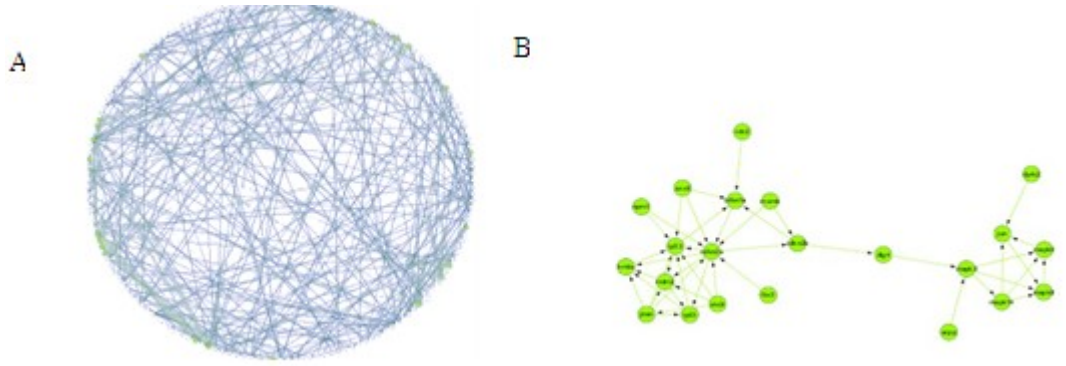

Figure 2 A: Network Of HIV-1 Has 164 Nodes, Its Clustering Coefficient Is 0.522, Network Diameter Is 11, It Has 11036 Shortest Paths And Its Percentage Is 41%, Characteristic Path Length Is 4.702, Average Number Of Neighbors Is 3.341.

B:core network has 22 nodes, its clustering coefficient is 0.569, network diameter is 7, it has 462 shortest paths and its percentage is 100%, characteristic path length is 3.156, average number of neighbors is 4.091.

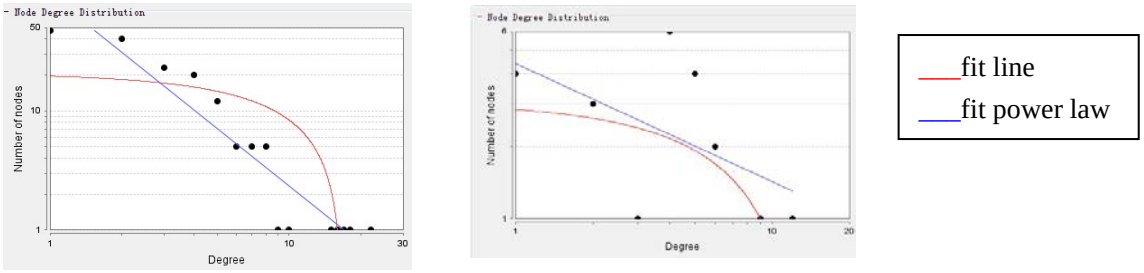

Figure 3 Nodes Degree Distribution. Network Of HIV-1(Left) Panel ;Core Graph(Right) Panel

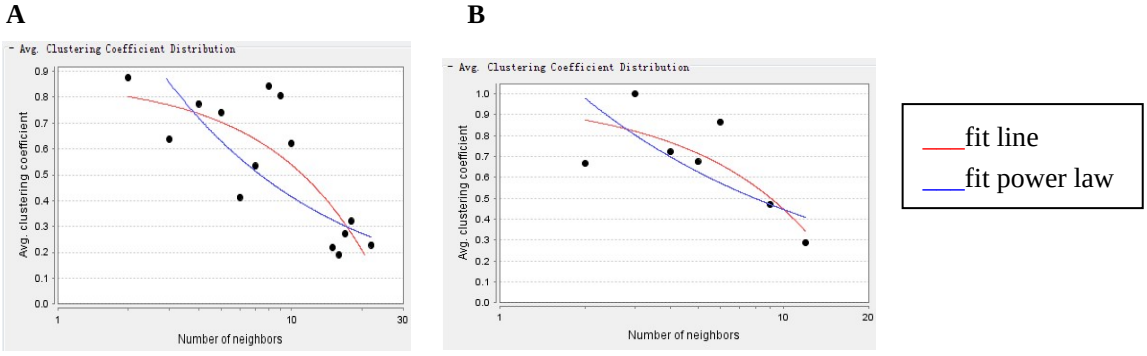

Figure 4 Clustering Coefficient Fit Line In The Form V=A+Bx Was Fitted,Power Law Has The Form $V=Ax^b$

A Network Of HIV-1 Coefficient Is 0.522; B Core Graph: Clustering Coefficient Is 0.569.

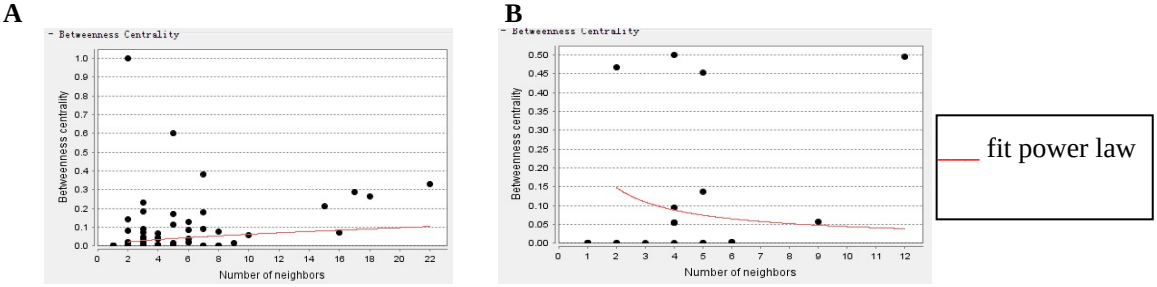

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Figure 5 Betweenness Centrality: Power Law Has The Form $V=Ax^b$ Coefficient As Follows:字体不同

A Network Of HIV-1: A=0.014,B=0.642,Correlation=0.169, R-Squared=0.056

B Core Graph:A=0.249,B=0.749,Correlation=0.212,R-Squared=0.033

R-Squared Is Computed On Logarithmized Values.

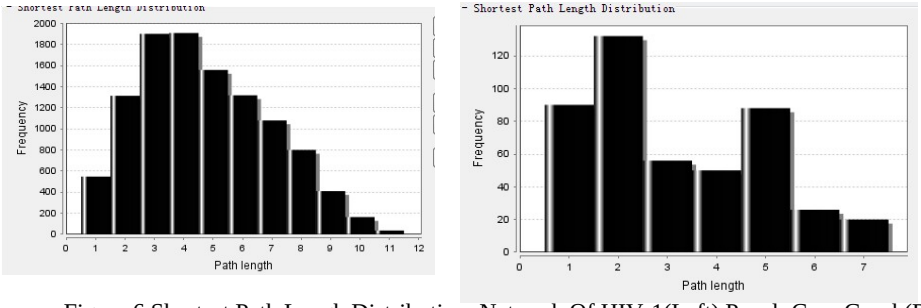

Figure 6 Shortest Path Lengh Distribution. Network Of HIV-1(Left) Panel; Core Graph(Right) Panel

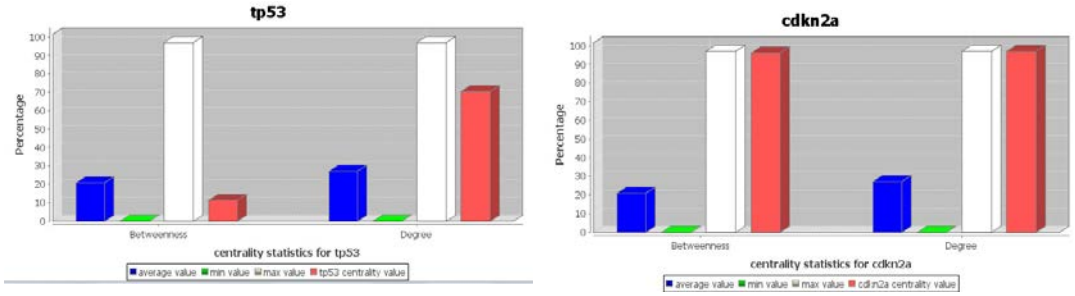

Figure 7 Tp53 :Node Degree Is 9(Left) Panel; Cdkn2a:Node Degree Is 11(Right) Panel

Conclusion: the degree of a node is much more bigger, its betweenness value is bigger, and the node is more important. So, cdkn2a is a potential drug target.

2.2. Methods :Core graph construction and Network Parameter Estimation

2.2.1 Algorithm for constructing core graph[3]: Let G(V,E) be a network, where V is the set of nodes of G and E is the set of edges of G. The algorithm starts with S=V, selects a node u with the minimum degree in G[S], removes u from S only if the graph defined on S\{u} remains a connected graph of G, and repeats the above steps for all nodes in S in order of their increasing degrees. Ues this method to construct the core graph of HIV-1 network shown in Fig 2 B.The network properties were computed using Cytoscape software (http://dip.doe-mbi.ucla.edu/dip/Main.cgi).

2.2.2 Network properties.

Graphs. A graph G=(V,E) is a set of nodes V and a set of edges $E \subseteq V \times V$. We consider undirected graphs: $(u,v) \in E$. The degree of a node in the network is the number of other nodes it connected to.

Clustering coefficient. The clustering coefficient was first defined by Watts and Strogatz [4]. The clustering coefficient, C, for a node is a notion of how connected the neighbours of a given node are to the other nodes (cliquishness) [5]. The average clustering coefficient for all nodes in a network is taken to be the network clustering coefficient. In an undirected graph, if a vertex v_i has k_i neighbors, k_i $(k_i - 1)/2$ edges could exist among the vertices within the neighbourhood (N_i). The clustering coefficient for an undirected graph G(V, E) (where V represents the set of vertices in the graph G and E represents the set of edges) can then be defined as

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$$C_i = \frac{2|\{e_{jk}\}|}{k_i(k_i-1)}; v_j, v_k \in N_i, e_{jk} \in E$$

The average clustering coefficient characterizes the overall tendency of nodes to form clusters or groups. C(k) is defined as the average clustering coefficient for all nodes with k links[5].

Characteristic path length. The characteristic path length, L, is defined as the number of edges in the shortest path between two vertices, averaged over all pairs of vertices. It measures the typical separation between two vertices in the network. Intuitively, it represents the network's overall navigability [5] .

$$L = \frac{\sum_{u,v \in G} d_G(u,v)}{\sum_{v_i \in G} v_i}$$

where d_G (u, v) is the shortest path between u and v in G.

Network diameter. The network diameter d is the greatest distance (shortest path, or geodesic path) between any two nodes in a network. It can also be viewed as the length of the 'longest' shortest path in the network.

$$d = \max_{u,v \in G} d_G(u,v)$$

where d_G (u, v) is the shortest path between u and v in G.

Betweenness centrality. The betweenness centrality is the measure of vertex within a graph. For a given graph G(V,E), with n vertices, the betweenness C_B (v) of a vertex v is defined as.

$$C_B(v) = \sum_{s \neq v \neq t \in V} \frac{\sigma_{st}(v)}{\sigma_{st}}$$

where δ_{st} is the number of shortest path from s to t, and $\delta_{st}(v)$ is the number of shortest paths from s to t that passes from vertex v.The betweenness centrality analysis was performed for both the networks [5] .

Power law distribution. For a given network the power law distribution states the probability that a given node has k links,which is given by equation p(k)~ k- λ , where λ is degree exponent.For smaller values of λ , the role of the 'hubs', or highly connected nodes, in the network becomes more important. For λ >3, hubs are not relevant, while for 2< λ <3, there is a hierarchy of hubs,with the most connected hub being in contact with a small fraction of all nodes. Scale-free networks have a high degree of robustness against random node failures, although they are sensitive to the failure of hubs [6]. The probability that a node is highly connected is statistically more significant than in a random graph[5].

3. CONCLUSION

By analyzing the HIV-1 network and its performance of dominating sets, as shown in Fig2 to Fig 6, we can get the following conclusions:_the dominant clustering coefficient is greater than HIV-1 network, the results of power law distribution and betweenness centrality are better than HIV-1 network.

The core graph shows the relationship between the degree of the node and betweenness centrality. As shown in Fig 7, the greater the degree of the node, the greater the value of betweenness, and the nodes have greatest degree might be a new drug target.

In this paper, the degree of tp53 and cdkn2a are respectively 9 and 11, are bigger than the other nodes. So, these two nodes are more important.The degree and betweenness value of those nodes are compared in Fig 7, and it can be concluded

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that:cdkn2a is a potential drug target.

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