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Gene-Gene Interaction Mapping Of Human Cytomegalic Virus through System Biology Approach

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Abstract

Systems biology is concerned with the study of biological systems, by investigating the components of cellular networks and their interactions. The objective of present study is to build gene-gene interaction network of human cytomegalovirus genes with human genes and other influenza causing genes which helps to identify pathways, recognize gene function and find potential drug targets for cytomegalovirus visualized through cytoscape and its plugin. So, genetic interaction is logical interaction between two genes and more than that affects any organism phenotypically. Human cytomegalovirus has many strategies to survive the attack of the host. Human cytomegalovirus infection of host cells induces cellular activation and disturbance of the cell cycle. Further functional analysis was done to know functionally active genes to cause infection and also these genes will be used as targets to prevent infection spread through virus and then ontology analysis was performed to those functionally active genes describes gene products in terms of their associated biological processes, cellular components and molecular functions by using clueGO Plugin.

Keywords: System biology; Functional analysis; Ontology analysis

Introduction

Systems biology underpinning inter and intra-cellular dynamical networks, by means of signal and system-oriented approaches, applying experimental high throughput and whole genome techniques, integrating computational methods with experimental efforts. Emergence, robustness and modularity are the three basic concepts that are crucial to understanding complex biological system [1]. The main aspect of system biology is translating the biological information into models [2]. Drug discovery and the design of multiple drug therapies and therapeutic gene circuits and complex engineering product are the applications of systems biology to medical practice [3]. Human cytomegalovirus (HCMV) is an enveloped DNA virus that, like other members of the herpes virus family, establishes lifelong latency following primary infection Cytomegalovirus. Cytoscape is an open source bioinformatics software platform for visualizing molecular interaction networks and integrating with gene profiles and other state data. Cytoscape is most commonly used for biological research applications. The tool is best used in conjunction with large databases of gene expression data, protein-protein interaction, protein-DNA interaction, and genetic interactions that are increasingly available for humans and model organisms [4]. Several useful plugins are available for Cytoscape to extend its capabilities for example network analyzer plug-in. The study of gene - gene interaction play an important role in the search for the cause of human disease and the main aim of establishment of this study is To Build and Analyse Gene-Gene Interaction Network of HCMV genes. The network of hcmv genes are used for further studies such as Functional and Ontology Analysis of HCMV genes.

Materials and Methods

Materials

Data source

Gene card is a database of human genes that provide information about their functions, genomic views, proteins and protein domains, transcripts, orthology, paralogs, their expression localization, interaction and involvement in pathway, disease and disorders on all known human genes. Total 129 genes (Table 1) have been extracted from gene card to build a network.

Gene name	GCID from gene cards	PMID
	GC11MO73386	
ENSG00000183214	GC06Pn31357	
ENSG00000235233	GC06P131410	
RSAD2	GC02P007005	
ENSG00000206206	GC06MK33264	
ENSG00000206279	GC06Mn3215	
ENSG00000227046	GC06Mj33207	
ENSG00000231617	GC06Mm33456	
MIR20A	GC13P092001	
DAXX	GC06MO33286	
ENSG00000206235	GC06MI32943	
ENSG00000206297	GC06Mn32741	

ENSG00000206299	GC06Mn32718	
ENSG00000223481	GC06Mk32767	
ENSG00000224212	GC06Mk32790	
ENSG00000225967	GC06Mi32773	
ENSG00000226173	GC06MI32966	
ENSG00000227816	GC06Mi32796	
ENSG00000228582	GC06Mj32703	
ENSG00000230705	GC06Mm32846	
ENSG00000232326	GC06Mo32879	
ENSG00000232367	GC06Mj32735	
ENSG00000237599	GC06Mm23815	
MIR17	GC13P092002	
TMEM147	GC19P036038	
GGH	GC08M063928	
LINC01194	GC05P012578	
MRGPRXI	GC11M018955	
MPZ	GC01M161274	
HNRNPH3	GC10P070090	
MICA	GC06P031373	
RAB11FIP4	GC17P029718	
CBR1	GC21P037442	
FKBP10	GC17P039968	
IL32	GC16P003153	
TMEM43	GC03P014142	
TRIM23	GC05M064885	
CX3CL1	GC16P057406	
DDX39A	GC19M014521	
LBR	GC01M2255899	
CAMKK1	GC17M003763	
CD69	GC12M010498	
CHAF1A	GC19P004402	
LILRB1	GC19P055085	
MICB	GC06P031465	
PDIA4	GC07M148700	
TAPT1	GC04M016162	
WDR26	GC01M224573	
ANXA2	GC15M060639	
CFLAR	GC02P201980	

ACLY	GC17M040023	
ACTL6A	GC03P179280	
AGTR2	GC0XP115216	
ANAPC10	GC04M145916	
ANAPC7	GC12M110810	
ANAPC5	GC12M121746	
CEBPA	GC19M033790	
EEF2K	GC16P022217	
EIF2AK3	GC02M088857	
IFI16	GC01P0158969	
KAT5	GC11P065479	
NUDT21	GC16M056463	
RAB11A	GC15P066018	
RAB1A	GC02M065297	
SPI1	GC11M049902	
TAP1	GC06M032812	
TAP2	GC06M032789	
THBS2	GC06M169615	
TLR3	GC04P186990	
DDX39B	GC06M031522	
ANPEP	GC15M090328	
CAMKK2	GC12M121675	
CD59	GC11M03721	
CDC23	GC05M137552	
DDB1	GC11M061066	
EGR1	GC05P137801	
EP400	GC12P132434	
HFE	GC06P026087	
HLA-G	GC06P029794	
MSR1	GC08M016009	
PSMB6	GC17P004699	
PSMB4	GC01P151372	
PSME3	GC17P040985	
RUVBL2	GC19P049497	
RUVBL1	GC03M127783	
TLR9	GC03M052255	
UBR5	GC08M103265	
CAMK2B	GC07M044225	

CAMK2A	GC05M149579	
CDC27	GC17M045195	
E2F1	GC20M032263	
EIF4A1	GC17P007476	
HSPA5	GC09M127997	
KPNA1	GC03M122140	
PML	GC15P074287	
PSMA3	GC14P058711	
PSMC6	GC14P053173	
PSMD3	GC17P038137	
RAN	GC12P131356	
SUMO1	GC02M203070	
THBS1	GC15P039873	
TRRAP	GC07P098475	
WT1	GC11M032365	
AGTR1	GC03P148415	
CAMK2G	GC10M075572	
CDK2	GC12P056360	
FLNB	GC03P057969	
GPT	GC08P145728	
HLA-C	GC06M031236	
HLA-DQA1	GC06P032595	
PSMD2	CG03P184016	
PSMC4	GC19P040477	
TLR2	GC04P154612	
IL10	GC01M206940	
IL4	GC05P132009	
STAT3	GC17M040465	
CAMK2D	GC04M114372	
HLA-A	GC06P030186	
HLA-DQB1	GC06M032629	
ICAM1	GC19P010381	
PIK3CG	GC07P106505	
IL6	GC07P022765	
MAPK1	GC22M022108	
CASP3	GC04M185548	
HLA-DRB1	GC06M032546	
NFKB1	GC04P103422	
CD55	GC01P207494	
MAPK14	GC06P035995	
TNF	GC06P031543	
TP53	GC17M007565	

Table 1: The table shows genes of HCMV with their respective GCID.

Tool

Cytoscape is an open source bioinformatics software platform and it provides basic functionality to layout and queries the network; to visually integrate the network with expression profiles, phenotypes, and other molecular states; and to link the network to databases of functional annotations [4,5]. Cytoscape has been used to construct HCMV network for Analysis of HCMV gene.

ClueGO is a cytoscape plug-in that enhances biological interpretation of large lists of genes. ClueGO integrates Gene Ontology (GO) terms as well as KEGG/BioCarta pathways and creates a functionally organized GO/pathway term network. **CluePedia** provides a comprehensive view on a pathway or process by investigating experimental [5].

Method

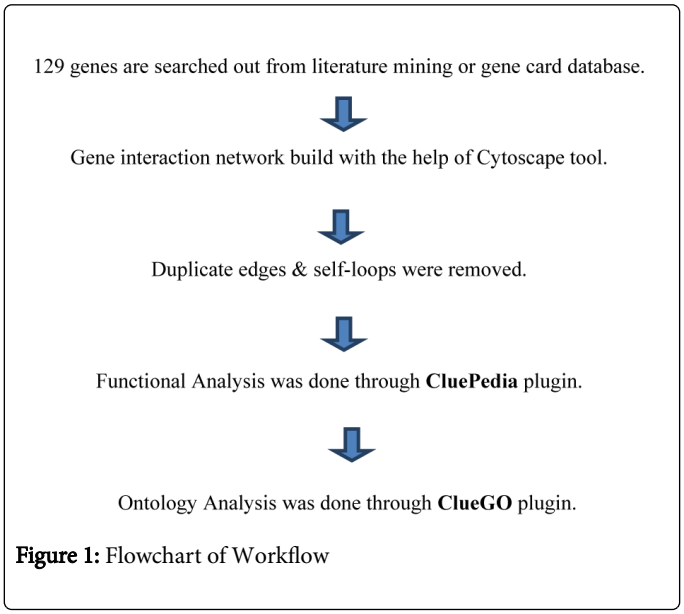

Figure 1: Flowchart of Workflow

Results and Discussion

The genes involved in infection spread through cytomegalo virus find through GeneCards database and various publish literature. Hence, gene-gene interaction network was built. The interaction network is imported through Cytoscape's web services option. However the study was aimed to find out the genes involved in cytomegalic infection in humans hence, genes from other species was removed but genes of influenza virus is in the network because patient's infected with influenza have elevated level of genes which are found to be causative agents of cytomegalovirus. Network containing self-loops, duplicate edges were removed and gene-gene interaction network contains 13923 genes and 35714 interactions (Figure 2).

The main objective behind genetic interaction network is to understand the relationship between the genotypes and phenotypes of individuals which could be important key for identifying genetic variants responsible for disease. Generally, unexpected phenotypic changes will occurred when two or more genetic variants will interact with each other. Hence, genetic interaction network will help to map affected gene and their related biological process or pathways to develop successful therapeutic strategies further.

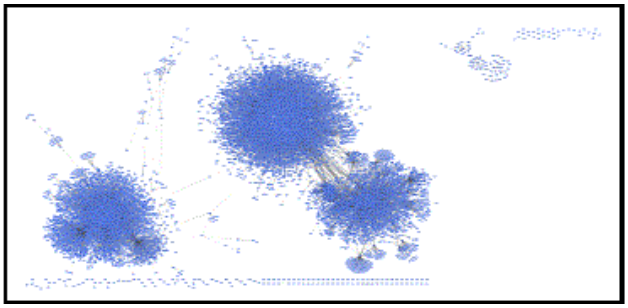

Figure 2: The above diagram shows gene-gene interation network of cytomegalo virus, influenza virus and human gene.

Analysis using CluePedia plugin

Although it was large gene interaction network and the research aimed to do functional analysis of gene dataset and this analysis was done through CluePedia plugin. Functional analysis helps to determine which gene is functional modules form list of genes of interest. CluePedia plugin helps to identify functionally participating group of genes in cytomegalic infection with their interaction type like expression, binding etc (Figure 3).

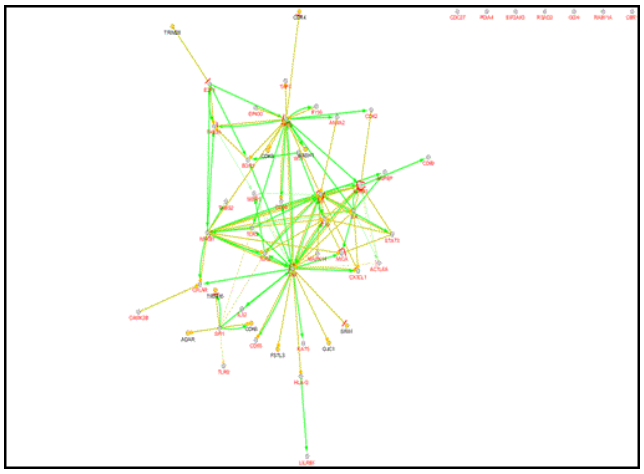

Figure 3: The above diagram shows enrichment analysis of gene through CluePedia plugin involved in infections spread through HCMV. Dark green line shows activation expression of gene and yellow line shows binding expression of genes.

Analysis through ClueGO Plugin

47 genes found functionally enriched among 129 genes and with the help of ClueGO plugin further analysis was done. Go term analysis was performed through ClueGo plugin and for categorizing 47 genes into GO term parameters taken as defaulted.

Go term analysis was performed through ClueGO plugin and for categorizing 47 genes into GO term, some parameter was set. Kappa (κ) Statistics is used to examine interrater and intrarater reliability of data in relation to clinical diagnosis or classification and assessment finding. These data require to access specific reliability that's why kappa statistics used. The range of possible values of kappa is from –1 to 1, though it usually falls between 0 and 1. Unity represents perfect agreement, indicating that the raters agree in their classification of every case. Zero indicates agreement no better than that expected by chance. A negative kappa would indicate agreement worse than that expected by chance [6].

The main aim of ontology analysis of functionally enriched genes is to know which gene upregulates and down regulates in certain biological process. ClueGO analysis performs automatically the calculation of the terms and groups significance. P-Value correction method is selected in ClueGO selection panel, then on the network and on the charts the corrected P-Value will be represented.

The terms and groups significance can be found in the ClueGo browser.
The chart showed in Figure 4; mark the level of the significance for terms and groups using:

1. **: if the term/group is over significant, P-Value <0.001.
2. *: if the term/group is significant, 0.001 <P-Value <0.05.
3. . (Dot): 0.05 <P-Value <0.01.

According to previous studies HCMV infection could disrupt mucosal surfaces, predisposing the patient to superinfection, or it could cause alterations in humoral and cell-mediated immunity [7]. In ontology analysis the over-significant pathways were found are **Cellular Senescence** is a process in which aging is occurred in single cell at individual level and there is an arrest of cell cycle to encounter oncogenic stress and infected cell will eliminated. **Cellular stress response** is a reaction in which structure and function of macromolecules is changed due to fluctuations in extracellular conditions of cells. In **Extrinsic Pathway for Apoptosis** the extrinsic ligand which can cause harm is leads to death by binding to TNF receptor and **Toll-Like Receptors Cascades** belong to a family of transmembrane proteins that can recognize and discriminate a diverse array of microbial antigens and also it plays important role in innate immunity system.

Somewhere these all over-significant process leads towards destruction of cell which can be oncogenic further and but in HCMV infection normal functions of all these pathways is disrupt primarily and afterwards infection can lead to chronic condition. Effective vaccines or drugs are not available for cytomegalo virus so by triggering these pathways and genes and their products which were affects the pathways successful therapeutic strategies will be developed.

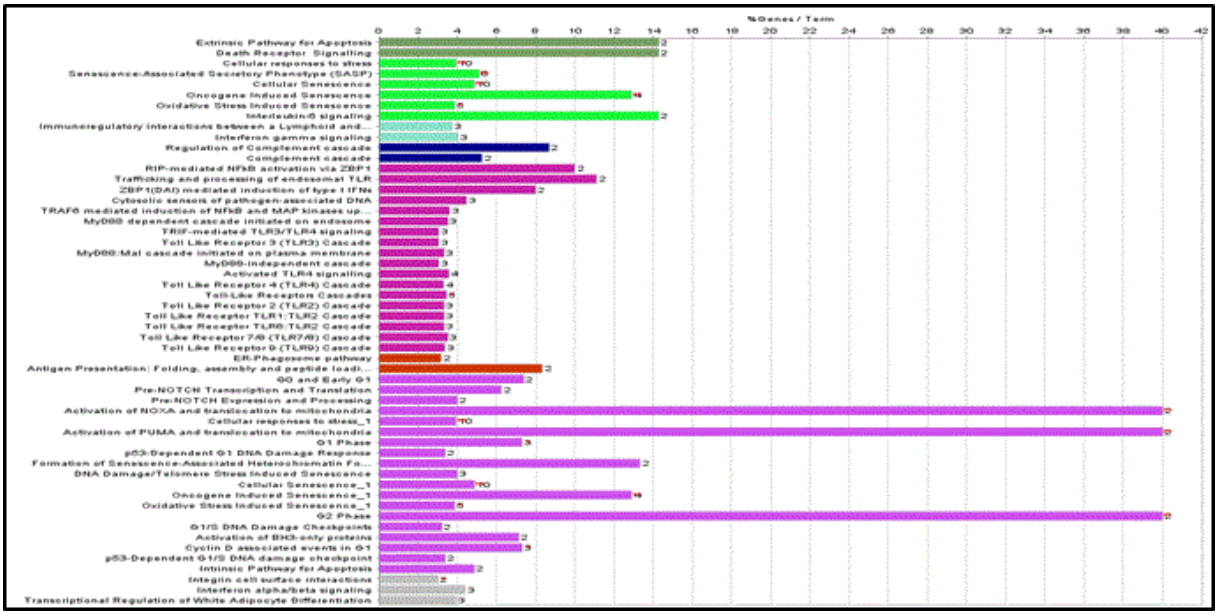

Figure 4: Graphical representation of biological processes found for 47 genes.

The below table shows biological process and name of genes involved in those biological process (Table 2).

Function	Groups	Group Genes
Cellular Senescence**	Group 1	CDK2|CDK4|CDK6|E2F1|EP400|IL6|MAPK14|NFKB1|STAT3|TP53
Cellular responses to stress**	Group 6	CDK2|CDK4|CDK6|E2F1|EP400|IL6|MAPK14|NFKB1|STAT3|TP53
Complement cascade**	Group 3	CD55|CD59
ER-Phagosome pathway	Group 5	HLA-G|TAP1
Extrinsic Pathway for Apoptosis**	Group 0	CFLAR|TNF
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell*	Group 2	CAMK2B|HLA-G|ICAM1|LILRB1
Integrin cell surface interactions	None 0	ICAM1|THBS1
Interferon alpha/beta signalling	None 1	ADAR|EGR1|HLA-G
Toll-Like Receptors Cascades**	Group 4	IFI16|MAPK14|NFKB1|TLR2|TLR3|TLR9
Transcriptional Regulation of White Adipocyte Differentiation	None2	CDK4|NFKB1|TNF

Table 2: The above table shows significant biological process founded for 47 genes.

Conclusion

The genetic interaction study of human cytomegalovirus was done using Cytoscape tool and its various plugins. This study focuses on building and analyzing the gene-gene interaction network for cytomegalovirus. Gene-gene interaction network was retrieve from Cytoscape web services and network contains 13923 nodes and 35714 edges of human gene and genes causing influenza infection. Functional analysis of HCMV genes found to spread disease was performed with the help of CluePedia plugin, a total of 47 genes were predicted in functional analysis. Ontology analysis of those 47 genes was performed through ClueGO plugin to predict significant biological processes.

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