Unique ability of pandemic influenza to downregulate the genes involved in neuronal disorders

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Abstract

Purpose

Pandemic influenza remains as a substantial threat to humans with a widespread panic worldwide. In contrast, seasonal (non-pandemic) has a mild non-lethal infection each year. The underlying mechanisms governing the detrimental effects of pandemic influenza are yet to be known. Transcriptomic-based network discovery and Gene Ontology (GO) analysis of host response to pandemic influenza, compared to seasonal influenza, can shed light on the differential mechanisms which pandemic influenza is employed during evolution.

Methods

Here, using microarray data of infected ferrets with pandemic and seasonal influenza (as a model), we evaluated the possible link between altered genes after pandemic infection with activation of neuronal disorders. To this end, we utilized novel computational biology techniques including differential transcriptome analysis, network construction, GO enrichment, and GO network to investigate the underlying mechanisms of pandemic influenza infection and host interaction.

Results

In comparison to seasonal influenza, pandemic influenza differentially altered the expression of 31 genes with direct involvement in activity of central nervous system. Network topology highlighted the high interactions of *IRF1*, *NKX2-1* and *NR5A1* as well as miRNA27A, miRNA19A, and miRNA17. *TGFB2*, *NCOA3* and *SP1* were the central transcription factors in networks. Pandemic influenza remarkably downregulated *GPM6A* and *GTPase*. GO network demonstrated the key roles of *GPM6A* and *GTPase* in regulation of important functions such as synapse assembly and neuron projection.

Discussion

For the first time, we showed that besides interference with cytokine/chemokine storm and neuraminidase enzyme, H1N1 pandemic influenza is able to directly affect neuronal gene networks. The possibility of application of some key regulators such as GPM6A protein, MIR128, and MIR367 as candidate therapeutic agents is discussed. The presented approach established a new way to unravel unknown pathways in virus-associated central nervous system (CNS) dysfunction by utilizing global transcriptomic data, network and GO analysis.

Keywords: Central nervous system (CNS) dysfunction; GPM6A; Gene Ontology Enrichment; Gene Ontology network; miRNA128; miRNA367; Pandemic influenza; Transcriptomic analysis; Gene networks

Introduction

Pandemic influenza, as the most detrimental type of influenza virus, has a proven record of mortality in human history, including Asiatic (Russian) flu in 1889 with 1 million deaths (Valleron et al. 2010), Spanish flu in 1918 with 20-100 million deaths (Mills et al. 2004), Asian flu in 1957 with 1-1.5 million deaths, Hong Kong flu in 1968 with 0.75-1 million deaths, and 2009 pandemic with 18000 deaths (Donaldson et al. 2009).

Susceptible groups to flu infection are children and old people, showing a range of viral infection signs such as fever, cough, petechial rash, respiratory disturbances, pulmonary disease, neurological disorder, and hematological alteration (Calitri et al. 2010). Neural complications, similar to Schizophrenia, Reye's syndrome, Parkinson, and Encephalopathy symptoms, can be seen in influenza infection (Toovey 2008). Also, other neural symptoms such as migraine exacerbation, exacerbation of myasthenia gravis, acute ischaemic stroke and seizure have been reported (Tan et al. 2010). It has been demonstrated that influenza A alters the expression of some genes involved in nervous system function (Mori et al. 2001; Fatemi et al. 2005).

Up to now, the observed effects of influenza on nervous system have been annotated solely to dysfunction in exuberant cytokine/chemokine response and neuraminidase enzyme (Lee et al. 2010; Maurizi 1985), and the possibility of involvement of the other pathways is extensively ignored. However, recently, it has been discussed that pandemic H1N1 viruses can employ additional mechanisms lined to stress and anxiety during the course of infection.

Availability of global transcriptomic data of host response to pandemic and non-pandemic (seasonal) influenza provides a unique opportunity to unravel the additional mechanisms which lead to success of pandemic influenza in host infection. Furthermore, recent developments in network analysis, Gene Ontology (GO) classification, and GO network offer new tools to discover the biological consequences of the observed alterations in gene expression profile.

The most comprehensive available data in the subject of host immunity against pandemic influenza is provided by Rowe et al., (2010). In the mentioned study, using ferret as experimental infection model, global gene expression profile of host immune response

against pandemic 2009-H1N1 A/California/07/2009 and seasonal A/Brisbane/59/2007 were obtained. (Rowe et al. 2010).

CCL2, *CCL8*, *CXCL7* and *CXCL10* (chemokines) along with the majority of interferon-stimulated genes were expressed early, correlated to lung pathology, and abruptly decreased expression on day 7 following infection of A/California/07/2009. They propose that lung pathology in humans occurs during the innate phase of host immunity and a delay or failure to switch to the adaptive phase may contribute to morbidity and mortality during severe 2009-H1N1 infections (Rowe et al. 2010). This data can be further analyzed in the context of network and GO annotations to dig into mechanisms underlying pandemic infection.

The concept of network-based medicine is based on this fact that rarely, a disease is a consequence of a single gene abnormality (Barabási et al. 2011). Network analysis by aggregating available information in the frame of networks provides the unique opportunities to unravel gene/protein interactions, correlations, and significant interactions which would be otherwise undiscovered and unexplored (Cruts et al. 2012). It should be noted that molecular components in a cell are functionally dependent; consequently, construction of statistically significant networks is much closer to the reality which happens within a cell. Network based analysis of gene expression data elaborates systematic view on disease emergence and also has been considered as an effective tool in gene discovery (Barabási et al. 2011; Stuart et al. 2003; Calvano et al. 2005; Wu et al. 2008). Network architecture (topology) can highlight the key genes (genes with higher number of interactions) as well as genes which connect different networks (Ebrahimie et al. 2014). Different approaches have been utilized for network discovery within a set of genes such as text (literature mining), co-expression analysis, promoter analysis, microRNA prediction, as well as visualizing GO interactions (Markowetz and Spang 2007; Stuart et al. 2003; Obayashi et al. 2013; Zhang and Horvath 2005; Ruan et al. 2010; Nikitin et al. 2003; Bakhtiarizadeh et al. 2014; Hosseinpour et al. 2012; Fruzangohar et al. 2014).

Similar to network analysis, GO analysis adds a new dimension in biological knowledge discovery from the bulk of differentially expressed genes (Fruzangohar et al. 2014; Fruzangohar et al. 2013). GO classification of significant up/downregulated genes is the first step in functional genomic analysis to interpret the transcriptomic data. GO enrichment analysis classifies genes/proteins based on the controlled universal vocabulary in 3 major categories of Biological Process, Molecular Function, and Cellular Component which greatly helps the researchers to reach the similar functional annotation language and understanding. Finding the key GO groups and selection of genes based on the significant GOs are novel and

reliable approaches in gene discovery as the selected genes are central in meaningful biological processes (Fruzangohar et al. 2013). Furthermore, comparison of GO enrichment of a given sample versus GO distribution of whole genome (as reference) by Fisher exact test (hyper-geometry approach) illustrates the differential functional groups in a particular sample. Furthermore, recent developments in constructing GO networks provide unique possibility to investigate the transcriptome in the context of functional interactions between different GO classes (Fruzangohar et al. 2014; Fruzangohar et al. 2013).

The aim of this study was to compare the differential effects of pandemic and non-pandemic influenza viruses on host functional genomics, in particular nervous system, in the context of GO enrichment, gene networks and regulatory mechanisms. To this end, microarray data of the effects of the pandemic virus, A/California/07/2009, and non-pandemic virus, A/Brisbane/59/2007, on *Canis lupus* (host) was employed. Up and downregulated genes, during the course of infection with pandemic or seasonal viruses, were computed and significantly altered genes related to nervous systems were determined. A variety of computational biology techniques including subnetwork discovery, network construction, GO enrichment, and GO network were utilized to shed light on the underpinning mechanisms of pandemic influenza and host interaction. For the first time, we found that apart from cytokine/chemokine storm and neuraminidase enzyme dysfunction, pandemic influenza activates other neuronal disorder pathways. Modulation of these genes can cause neuronal disorder in patient with pathogenic H1NI influenza virus.

Materials and methods

Data collection

Affymetrix-based microarray data of ferret, as mammalian model, after injection with seasonal (non-pandemic, A/Brisbane/59/2007) and pandemic influenza (A/California/07/2009) (Rowe et al. 2010) were downloaded from GEO repository of NCBI database (GEO number: GSE17079). In this experiment RNA was extracted from lung tissue of ferret and the host immune responses during the infection with seasonal A/Brisbane/59/2007 and 2009-H1N1 A/California/07/2009 were profiled by Affymetrix Gene Chip Canine Genome 2.0 Array.

Expression analysis

The plan of the original experiment by Rowe et al., (2010) was in time series frame. In this study, this plan disregarded and the data pooled together to generate two separate treatments: (1) infection with pandemic (A/California/07/2009 strain), and (2) infection with non-pandemic (A/Brisbane/59/2007 strain). Each treatment had 15 replicates (expression CEL files). The employed analytical scheme is presented in Figure 1.

We normalized the downloaded CEL files of 3' expression array by Expression Console software (Affymetrix, USA) based on RMA (Robust Multichip Analysis) algorithm as described previously (Hosseinpour et al. 2012; Alisoltani et al. 2014). Two sample Bayesian t-test was used to select the genes with significant differential expression at $p=0.05$ between two treatments [infected host with pandemic versus non-pandemic (seasonal) virus]. It has been discussed that Bayesian based statistics have better performance with consistent Type I error rates, compared to the other methods (Fox and Dimmic 2006; Baseri et al. 2011). In addition to statistical significance, we also calculated Symmetric Fold Change (SFC). SFC represents upregulation with positive and downregulation with negative values. Analyses carried out by Flexarray package (Mc Gill University, Canada) as described previously (Hosseinpour et al. 2012; Alisoltani et al. 2014). Finally, genes with significant differential expression ($p=0.05$) and $SPF > +2$ or $SPF < -2$ were selected as upregulated/downregulated genes.

Based on the above mentioned characteristics, we found 23 downregulated genes ($p=0.05$, $SPF < -2$) as well as upregulated 127 genes. Upregulated and downregulated genes were further investigated based on literature, available databases [Uniprot (<http://www.uniprot.org/>) and Gen Cards (<http://www.genecards.org/>) (Safran et al. 2002)] as well as GO classification using Comparative GO web application (Fruzangohar et al. 2013) to

illustrate the ones which possibly are involved in neuronal disorders and exuberant cytokine responses. As it has been discussed in results, 4 downregulated genes (out of total 23 downregulated) and 27 upregulated genes (out of total 127 upregulated) were related to nervous system. These genes, particularly 4 downregulated genes, were used for further GO and network analysis .

Subnetwork discovery and construction of pandemic influenza-associated nervous gene network

In addition to the common expression analysis (described above), novel approaches of subnetwork discovery and network analysis were used to investigate whether neuronal disorder related up/downregulated genes can contribute in generation of statistically significant neuronal subnetworks or not.

We used RESNET database of Pathway Studio 10 (Elsevier) (Nikitin et al. 2003) which is an enriched database of mammalian gene/protein/small RNA interaction. The database contained new aliases for human genes, miRNAs, other non-coding RNAs as well as entries from other mammals. Extensive literature mining and literature based rule discovery by MedScan natural language processing (Novichkova et al. 2003) as well as microRNA target prediction and more importantly, the developed statistics for determining statistically significant (such as Fisher exact test) based on Gene Set Enrichment (GSE) approach (Subramanian et al. 2005) provided the opportunity to further investigation of significantly interactive networks within the altered genes by Pathway Studio Package. Furthermore, database is not restricted to a particular interaction and contains a wide range of interactions including promoter binding, mol transport, regulation, expression, protein modification, binding, mol synthesis, chemical reaction, direct regulation, miRNA effect, and small molecule (Nikitin et al. 2003). GSE is a robust method in detection of statistically significant subnetworks which up/downregulated genes can generate (Subramanian et al. 2005; Ebrahimie et al. 2014). Using the imported list of genes/miRNAs as input, GSE statistically examines the enrichment of different subnetworks within the collection of networks (gathered by literature mining in RESNET database of Pathway Studio) at $p=0.05$ using reliable statistics such as Fisher's exact test.

To construct regulatory gene network, neighbor joining algorithm at expansion = 1 was used to link network elements (entities) based on different deposited relationships at RESNET database and up/downregulated genes as inputs as described previously (Hosseinpour et al. 2012; Alisoltani et al. 2014). Both upstream and downstream were selected as directions of

each entity. A range of entities such as small molecules, cell process, pathogenesis, functional class as well as various types of relation such as expression, regulation, binding, moltransport, miRNA effect, etc. were considered to provide a comprehensive approach of influenza related pathways. The excel format of each network, containing all relations and entities of the network were recorded and presented as supplementary files.

GO regulatory network construction

In addition to the above mentioned networks, using statistically significant up/downregulated genes, we predicted a novel types of regulatory networks based on GO interactions using Comparative GO (<http://turing.ersa.edu.au/BacteriaGO>) (Fruzangohar et al. 2014). In this type of network, instead of investigating relationships between genes, the genes transform to GO terms of Biological Process. Then, regulatory relationships were constructed between GOs (of Biological Processes) based on interactions extracted from Gene Ontology database (<http://www.geneontology.org/>) (Ashburner et al. 2000; Consortium 2004). The extracted relationships were deposited in internal database of Comparative GO portal (Fruzangohar et al. 2014; Fruzangohar et al. 2013). For the given gene sample of up/downregulated genes of neuronal-related genes, Comparative GO built a GO DAG (Directed AcyclicGraph) network, based on regulatory relationships. Then, in order to infer new relationships from available relationships, the initial GO was expanded to include new GO nodes interacting with parental nodes (Fruzangohar et al. 2014). The GO interaction network was visualized by Cytoscape plugin (Shannon et al. 2003) implemented in Comparative GO portal (Fruzangohar et al. 2014).

An important note regarding GO network is that GO networks incorporates alternative splicing in the network, as a GO with either more genes or more transcripts has the bigger size circle (diameter) compared to the GOs with less number of genes and alternative transcripts. It should be noted that the higher number of splicing indicates more activity and can be assumed as higher index of importance.

Comparison the GO distribution of a sample verses genome distribution

We compared (at $p=0.05$) the GO enrichment of up/downregulated gene samples and their alternative transcripts verses genome using hyper-geometric distribution approach by Comparative GO web application (Fruzangohar et al. 2013). This analysis helps us to investigate the specific functions/pathways that our gene sample in involved in GO terms of biological process, molecular function, and cellular component. Hyper-geometry is based on

Fisher exact test to find the differential distribution of GO enrichment within our sample compared to genome (as reference/control).

Results

Monitoring the differential response of host system to pandemic influenza compared to seasonal (non-pandemic) influenza

The results showed that pandemic influenza (A/California/07/2009) infection differentially modulates 31 host genes (27 genes up and 4 genes downregulated) associated with nervous system whereas seasonal influenza (A/Brisbane/59/2007) was not able to alter them. The list of the downregulated genes and their descriptions regarding nervous system are presented in Table 1. Interestingly, these genes play important roles in neuronal communication and regulation such as neuronal differentiation, neuronal plasticity, neurite and filopodia outgrowth, synapse formation, establishment and maintenance of neuronal connections (Table 1).

Subnetwork discovery: a clue for analyzing differential impact of pandemic influenza on host system in comparison to non-pandemic influenza

It is possible that each gene acts independently, but commonly, the genes interact with each other and form subnetworks. These subnetworks join together based on the shared elements (commonly transcription factors and microRNAs) and form the networks. Consequently, the first step in network analysis is subnetwork discovery which is finding the statistically significant subnetworks within the list of differentially expressed genes. We investigated subnetworks using a range of interactions such as miRNA interaction, direct and indirect regulation, chemical interaction to increase the chance of discovery of activated subnetworks. Statistically significant subnetworks which can be generated by upregulated genes are presented in Supplementary 1. Mitogen-activated protein kinase, calcium-independent protein kinase C, and SP1-interacting genes are important subnetworks. *SP1* was the major transcription factor for many genes regulations such as *NR5A1*, *FN1*, *IRF1*, and *NKX2-1*.

In this study, our attention was majorly paid to the downregulated genes. Statistically significant subnetworks which can be generated by downregulated genes are presented in Table 2.

As presented in Table 2, microRNAs play the key role in forming the subnetworks of downregulated genes. In particular, microRNAs such as *MIR367*, *MIR15B*, *MIR128*, and *MIR325* cause significant subnetworks which interact with proteins such as *GPM6A*, *EVI5*, *PCDHAC2*, and *ARPP21*. Subnetworks of *MIR367*, *MIR15B*, and *MIR128* are presented in

Figure 2. Interestingly, *EVI5* contributes in two microRNA subnetworks and is under the control of MIR367 and MIR128. It can be stated that when a gene is under control of more regulators, it possibly play key functions. As presented in Table 1, *EVI5* commonly has expression in brain and adrenal.

Network analysis of host neuronal related genes specific to pandemic influenza infection

Network analysis carried out to find the possible networks of host up and down which specifically are activate during pandemic influenza infection. One of the key benefits of network prediction is finding the central network genes (hubs). These hubs have the highest number of interactions with other genes which commonly indicates the higher importance/function of these genes.

The predicted network based on neighbor joining algorithm is presented at Figure 3. The relations of this network and their references are presented in Supplementary 2. Network shows that apart from some genes such as *CCBL1*, *RNF10*, *SF1* and *LAPTM5*, the others had complex interactions together. According to the interaction network of Figure 3, *FN1* is an upregulated gene with the high number of interactions with the other genes; along with *IRF1*, *NKX2-1*, and *NR5A1* genes. Interestingly, upregulation of FN1 gene can lead to disorders in many processes (Villani et al. 2007).

Another important subject in gene networking was the interactions between the nodes. The crosstalk between six nodes is presented in Figure 4A and Supplementary 3 demonstrating that *NCOA3* and *TGFB2* join the 4 other nodes together. The expression target analysis between these genes (Figure 4B and Supplementary 4) showed that the *SPI* is in the center of interactions.

Induction of severe cytokine/chemokine storm related network by pandemic influenza

Further study of genes which particularly induce by pandemic influenza (Table 1) showed that in addition to neuronal disorders, some of these genes are involved in cytokine/chemokine storm as well. It seems that there is a direct crosstalk between genes involved in cytokine/chemokine storm (after virus infection) and the genes involved in neuronal disorders as upregulated genes of *YWHAE*, *AES*, and *IRF1* and downregulated gene of *EVI5* are shared. These genes can cause cytokine/chemokine storm on one hand and cause neuronal disorders the other hand. Crosstalk between genes involved in neuronal disorders and cytokine storm is presented at Figure 5. Interestingly, some genes of cytokine storm process such as *HNRNPM*, *CDK9*, *TSC22D1*, and *KPNA2* directly interact with the genes

involved in neuronal disorders (Figure 5). Relations of this network and its references are presented in Supplementary 5.

GO regulatory network of host genes which merely downregulate by pandemic influenza compared to seasonal (non-pandemic) influenza

Figure 6 shows GO regulatory network of host genes which merely downregulate by pandemic influenza (compared to seasonal non-pandemic influenza). GO regulatory network represent 3 types of information: (1) regulatory relationships between GO terms and their associated genes presented by directed edges of the circles, (2) enrichment (magnitude) level of each GO term which is presented by diameter of circles, and (3) finally, the genes linked to each GO term (Fruzangohar et al. 2014). Furthermore, network topology highlighted the GOs and their associated genes which have the highest number of interactions with other GOs. Based on the network topology, these genes locate on the centre of network. As higher network interaction can be assumed as higher importance index, GO and its corresponding genes, located at the centre of the network can be assumed to play more central regulatory function in the process.

The predicted GO network (Figure 6) shows that 2 functional groups of “positive regulation of filopodium assembly” and “positive regulation of RabGTPase activity” are located in the centre of network and have the highest number of connections (interactions) with the other GOs. Interestingly, “positive regulation of filopodium assembly” contains *GPM6A*. *GPM6A* is remarkably downregulated (more than 5 fold change) in host after pandemic influenza infection (Table 1) whereas non-pandemic influenza could not downregulate this gene. GO harboring *GPM6A* has interactions with other GOs including synapse assembly, neuron projection, and neural retina development. GTPase activity is also located at the centre of network and has considerable number of interactions with other GOs such as synapse assembly and neuron projection (Figure 6).

Comparison of GO distribution of host neuronal related genes which solely downregulate by pandemic influenza

Comparison of GO enrichment of downregulated genes and their alternative transcripts verses GO distribution of whole genome by Fisher exact test (hyper-geometry) in 3 levels of “Biological Process”, “Molecular Function”, and “Cellular Components” is presented at Figure 7.

Interestingly, in the term of Biological Process, significantly downregulated functions by pandemic influenza (and their corresponding genes) were related to GO terms such as synapse assembly, positive regulation of filopodium assembly, neuron projection, and neural development (Figure 7A). Due to remarkable downregulation of these genes after pandemic infection, compared to non-pandemic infection, it can be concluded that the host infected with pandemic influenza has significantly lower synapse assembly, positive regulation of filopodium assembly, neuron projection, and neural development.

In “Molecular Function” term, downregulated genes (and their corresponding transcripts) enriched GOs such as calcium ion binding, calcium channel activity, and GTPase activity (Figure 7B). Regarding down regulation of these genes after pandemic influenza infection, infected host with pandemic influenza has lower calcium ion binding, calcium channel activity, nucleotide binding activity. Regarding the key role of calcium signaling and calcium channel activity in understanding the message and rapid response, it can be concluded that infected cells with pandemic influenza have lower efficiency in signal transduction, understanding response, and regulating host immune response.

In “Cellular Component, downregulated genes belong to the neuron cell body, integral membrane, membrane, and filipodum (Figure 7C). In other words, pandemic influenza targets and decreases the integral membrane and neuron body and hinders their development.

Discussion

While seasonal influenza has a mild infection with a low mortality, pandemic influenza is able to transmit easily between people, spread globally, with high pathogenicity and mortality. As example, 2009 H1N1 influenza A spread globally to over 116 countries. The understanding layer of the differential and successful evolution of pandemic influenza is yet to be known. The evolution of pandemic has occurred in respect to host response system. Consequently, the study of genes modulated in host transcriptome by pandemic influenza compared to seasonal non-pandemic influenza can provide valuable information in pandemic route of evolution. While up to now, more attention has been paid to the study of upregulated genes, this study documents the importance of analyzing downregulated genes in unraveling host response and pathogen evolution. It should be noted that modulation of a gene in host transcriptome can be a positive (as the host defense mechanism) or negative (as the host-breaking mechanism by pathogen).

In this study, we showed that pandemic influenza, significantly downregulate some genes related to neural disorders, in particular *GPM6A*. It has been recently reported that mutation in *GPM6A* can result in claustrophobia (El-Kordi et al. 2013). Regarding the polygenic nature of neural disorders, the fact that *GPM6A* is able to cause claustrophobia disorder highlights its importance. The *GPM6A* encodes the glycoprotein M6A that associated with the differentiation and neuronal migration of neurons derived from undifferentiated human stem cells (Michibata et al. 2009). Association of the *GPM6A* with the subgroup of schizophrenia patients reinforces the key role of this gene in regulation of CNS (Boks et al. 2008). Another study showed that the expression of this gene downregulates in chronic stress (Cooper et al. 2009). Therefore it can be concluded that pandemic influenza virus infection may cause chronic stress by *GPM6A* dysfunction. Because of the key role of this gene in neuronal disorders, downregulation of this gene may be the main reason for neurological disease after pandemic influenza infection. Another downregulated gene is the *EVI5* gene that encodes the ecotropic viral integration site5 protein or NB4S (Roberts et al. 1998). The *EVI5* has main role in mitosis and cell cycles (Eldridge et al. 2006), and a potential risk factor in multiple sclerosis (D'Netto et al. 2009).

Other downregulated genes, *PCDHAC2* and *ARPP21D*, were connected together by MIR15B and have major roles in nervous system functions. *PCDHAC2* is involved in the modulation of synaptic transmission and generation of specific synaptic connections (Frank and Kemler 2002). *ARPP21D*, encodes the 21KD cAMP regulated phosphoprotein. This protein is enriched in

cerebellar cortex of brain and has main roles in CNS function and diseases such as Alzheimer's disease (Hipfel et al. 2003). *PCDHAC2* interact in the network with *PSAP* (upregulated gene) by MIR19A and with *IRF1* (upregulated gene) through MIR17. *PSAP* encodes Saposin C protein and has several neuronal effects, including neuronal outgrowth stimulation, neuron preservation, and nerve regeneration enhancement (Chu et al. 2005). *IRF1* is a transcription factor with a main role in CNS and involved in the pathogenesis of multiple sclerosis and experimental autoimmune encephalomyelitis (Ren et al. 2011). Also, the downregulated gene, *ARPP21D*, interacted in the network with upregulated *MARK2* (by MIR214) that involves in regulation of dendrites development in hippocampal neurons (Terabayashi et al. 2007).

Within the upregulated genes by pandemic influenza, *FNI* and *IRF1* had key positions and more interactions. *FNI* encodes fibronectin1 protein that has main roles in induction of neuronal adhesion proteins and neurite outgrowth (Choung et al. 2002). *IRF1* is another upregulated gene which encodes for interferon regulatory factor1 that is involved in the pathogenesis of multiple sclerosis and experimental autoimmune encephalomyelitis (Ren et al. 2011).

Downregulated genes were further investigated by three quality based functional genomics analysis (network discovery, GO enrichment, and GO network) to unravel the molecular networks and functional groups which these genes can attend, providing a more reliable method for identifying the central genes and study of systems biology. As quality based analyses methods, these approaches provided new knowledge regarding the interaction between genes and prevents false positive significant expression (quantity based method) which is the common problem in expression analysis (Lawrence et al. 2013). It should be noted that expression level alone cannot be announced as the sole criterion of gene significance whereas some genes with lower expression levels (such as transcription factors and microRNAs) play a prominent role in systems biology (Fruzangohar et al. 2014; Fruzangohar et al. 2013; Mahdi et al. 2013; Bakhtiarizadeh et al. 2013).

In particular, GO regulatory network showed high performance and pointed out (GOs containing *GPM6A* and *GTPase* as the central nodes interacting with important GOs of synapse assembly, neuron projection, and neural retina development. Compared to the common gene networks, GO regulatory networks can identify the key functional genomics based interactions in a broader sense (Fruzangohar et al. 2014). Classification of a large number of genes in a small number of GO classes and visualizing the GO networks can remarkably decrease the network complexity

and, more importantly, offers a new approach for gene selection by considering the genes which contribute to central nodes in GO regulatory networks

Downregulating GOs related to synapse assembly, calcium binding and calcium channel activity, neuron projection, and neuron membrane development by pandemic influenza is a major finding. Neural cell division does not progress after birth in the majority of mammals. However, interestingly, neuron development is an ongoing process where the neural membrane develops dendritic projection. More developed dendritic projection induce more advanced dendritic network which allows better communication and neural signal processing between neurons. In diseases such as depression, a less developed neural (dendritic) network is a common phenomenon. Calcium plays important regulatory roles in all brain activities such releasing the majority of neurotransmitters, long term memory, and development of synaptic connections (Armstrong and Hille). Calcium transportation occurs via calcium channels whereas in neural disorders, less activity of calcium channels is commonly observed (Armstrong and Hille). GTPase modulate the neural signals in dendritic junctions (Hille 1992). Both GTP and Ca^{++} related activities function in generation and modulation of effective neural signals.

Interestingly, pandemic influenza targets these key players (calcium channels, synaptic projection, and neural membrane development) to interfere neural development and synaptic transmission. In simple words, pandemic influenza makes the host less neurologically reactive and possibly depressive. In this manner, the host cannot effectively react to influenza infection. This can be assumed as one of the reasons of the observed depression during influenza infection. It should be noted that the non-pandemic (seasonal) has not this CNS-related capability.

This study has high potential to be used by clinicians. Due to crosstalk between pandemic influenza and CNS dysfunction diseases such as depression, Alzheimer's disease, claustrophobia, *GPM6A* and *GTPase* can be further investigated as therapeutic drugs for treatments of patients with severe pandemic influenza. Low expression level of genes/proteins such as *GPM6A*, *EV15*, *ARPP21*, *PCDHAC2*, and reversely, high level of microRNAs such as *MIR367*, *MIR128-1*, and *MIR15B* can be used for prognosis of neuronal disorders in the patients with pandemic influenza virus.

Conclusion

In conclusion, the results of this study showed that pandemic influenza virus is evolved differentially, (compared to non-pandemic influenza), to interference neural development and synaptic transmission through downregulations of key proteins of calcium channels, synaptic projection, and neural membrane. The neuronal disorder network has interactions and crosstalk with previously known cytokine/chemokine storm pathway.

Virus-associated central nervous system (CNS) diseases have mainly been studied in terms of cytokine/chemokine responses and neuraminidase enzyme dysfunction. The involvement of the other pathways is not yet discovered. The developed approach offers a new way to search for other possibilities to unravel unknown pathways in CNS dysfunction by utilizing global transcriptomic data, network and GO analysis.

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Tables

Table 1. The host genes which solely modulated (upregulated/downregulated) in response to pandemic influenza virus compared to seasonal /non-pandemic influenza)

Gene symbol	Gene title	Relation to Nervous system	Symmetric fold change *	Host response to pandemic influenza
<i>GPM6A</i>	Glycoprotein M6A	Involved in neuronal differentiation, plays a role in neuronal plasticity, involved in neurite and filopodia outgrowth, filopodia motility and probably synapse formation (Michibata et al. 2009)	-5.22	Down
<i>EVI5</i>	Ecotropic viral integration site5	Expressed in a wide range of tissues including brain and adrenal (http://www.uniprot.org/uniprot/O60447)	-2.11	Down
<i>PCDHAC2</i>	Protocadherin alpha subfamily C2	involved in the establishment and maintenance of specific neuronal connections in the brain (Frank and Kemler 2002)	-2.2	Down
<i>Arpp-21</i>	CAMP regulated phosphoprotein ,21KD	Act as a competitive inhibitor of calmodulin-dependent enzymes such as calcineurin in neurons (http://www.uniprot.org/uniprot/Q9UBL0)	-2.09	Down

*Negative sign shows downregulation.

Table 2. Statistically significant subnetworks generated by specifically downregulated genes by pandemic influenza compared to non-pandemic influenza

Name	Total # of Neighbors	Gene Set Seed	Overlap	Percent Overlap	Overlapping Entities	p-value	Jaccard similarity	Hit type
Neighbors of Mir367	16	Mir367	2	11	GPM6A;EVI5	0.00	0.11	Regulation
Neighbors of MIR15B	170	MIR15B	2	1	PCDHAC2;ARPP21	0.00	0.01	Regulation
Neighbors of EVI5	3	EVI5	1	25	EVI5	0.00	0.14	Regulation
Neighbors of ARPP21	3	ARPP21	1	25	ARPP21	0.00	0.14	Regulation
Neighbors of GPM6A	6	GPM6A	1	14	GPM6A	0.00	0.10	Regulation
Neighbors of Mir325	6	Mir325	1	14	ARPP21	0.00	0.10	Regulation
Neighbors of MIR128-1	414	MIR128-1	2	0	EVI5;ARPP21	0.00	0.00	Regulation
Neighbors of MIR128-2	18	MIR128-2	1	5	ARPP21	0.00	0.05	Regulation
Neighbors of ZDHHC17	21	ZDHHC17	1	4	GPM6A	0.00	0.04	Regulation
Neighbors of PPP1R1B	44	PPP1R1B	1	2	ARPP21	0.01	0.02	Regulation
Neighbors of Mir182	54	Mir182	1	1	EVI5	0.01	0.02	Regulation
Neighbors of Mir182	62	Mir182	1	1	EVI5	0.01	0.02	Regulation
Neighbors of MIR217	87	MIR217	1	1	GPM6A	0.02	0.01	Regulation
Neighbors of MIR185	91	MIR185	1	1	PCDHAC2	0.02	0.01	Regulation
Neighbors of MIR133B	94	MIR133B	1	1	GPM6A	0.02	0.01	Regulation
Neighbors of MIR367	108	MIR367	1	0	GPM6A	0.02	0.01	Regulation
Neighbors of CARM1	109	CARM1	1	0	ARPP21	0.02	0.01	Regulation
Neighbors of DRD1	180	DRD1	1	0	ARPP21	0.03	0.01	Regulation
Neighbors of MIR221	218	MIR221	1	0	PCDHAC2	0.04	0.00	Regulation
Neighbors of DRD2	223	DRD2	1	0	ARPP21	0.04	0.00	Regulation
Neighbors of PLK1	240	PLK1	1	0	EVI5	0.05	0.00	Regulation
Neighbors of	246	NGF family	1	0	ARPP21	0.05	0.00	Regulation

NGF family								
Neighbors of MIR15A	262	MIR15A	1	0	ARPP21	0.05	0.00	Regulation

Figure Caption

Figure 1. Analyzing workflow of determining differential evolution of pandemic influenza (A/California/07/2009), compared to seasonal influenza (A/Brisbane/59/2007), in altering mammalian host immune response.

Figure 2. Significant microRNA based subnetworks generated by the genes. Network for up and downregulated genes involved in neural disorder host neuronal related genes specific to pandemic influenza infection.

Figure 3. Network for up and downregulated genes involved in neural disorder specific to pandemic influenza infection. The orange box shows that the gene is upregulated. The green box shows that the gene is downregulated. The blue box represents the gene which is added by network analysis. Different lines (in the term of color and type) show different types of interactions which is schematically explained in Figure.

Figure 4. Interactions between nodes of host up/downregulated genes by pandemic influenza. A: Crosstalk between *FN1*, *IRF*, *NKX2-1*, *NR5A1* B: Expression target analysis between *FN1*, *IRF1*, *NKX2-1*, and *NR5A1*. The orange box shows that the gene is upregulated. The green box shows that the gene is downregulated. The blue box represents the gene which is added by network analysis. Different lines (in the term of color and type) show different types of interactions which is schematically explained in Figure.

Figure 5. Crosstalk between genes involved in neuronal disorders and cytokine storm.

Figure 6. Gene Ontology (GO) regulatory network of host genes which merely downregulated by pandemic influenza compared to seasonal (non-pandemic) influenza. Size of circles is the number of genes and their splicing variants in each Gene Ontology group.

Figure 7. Gene Ontology (GO) distribution of host neuronal related genes which solely downregulate by pandemic influenza verses GO distribution of genome in terms of (A) Biological Process, (B) Molecular Function, and (C) Cellular Component.

Supplementary caption

Supplementary 1. Subnetworks enriched with 27 gene which solely modulate (up/downregulate) in response to pandemic influenza virus compared to seasonal (non-pandemic) influenza.

Supplementary2. Relations of network for up and downregulated genes involved in neural disorder specific to pandemic influenza infection.

Supplementary 3. Relations of interactions between nodes (Crosstalk between FN1, IRF, NKX2-1, NR5A1) of host up/downregulated genes by pandemic influenza.

Supplementary 4. Relations of interactions between nodes (Expression target between FN1, IRF1, NKX2-1, NR5A1) of host up/downregulated genes by pandemic influenza.

Supplementary 5. Relations of crosstalk between genes involved in neuronal disorders and cytokine storm.

A

B

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