eJBio

Electronic Journal of Biology, 2022, Vol.18(9): 1-11

Identification of Potential Drug for Dengue Hemorrhagic Fever by Network-Based Drug Reprofiling Approach

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Citation: Praveenkumar KS, Sekar G, Sri Kavya MV, Rahman WSWA, Shahidan WNS, et al. (2022) Identification of Potential Drug for Dengue Hemorrhagic Fever by Network-Based Drug Reprofiling Approach. Electronic J Biol, 18(9): 1-11

Received date: April 20, 2022, Manuscript No. IPEJBIO-22-13259; **Editor assigned date:** April 25, 2022, PreQC No. IPEJBIO-22-13259 (PQ); **Reviewed date:** May 10, 2022, QC No. IPEJBIO-22-13259; **Revised date:** June 20, 2022, Manuscript No. IPEJBIO-22-13259 (R); **Published date:** July 02, 2022, DOI: 10.36648/1860-3122.18.9.041

Research

Abstract

Dengue fever can progress to Dengue Hemorrhagic Fever (DHF), which is a more serious and occasionally fatal form of the disease. The patient may acquire warning indications of serious disease about the time the fever begins to reduce (typically 3–7 days following symptom onset), and there are currently no effective antivirals available. Drug repurposing is emerging as a novel drug discovery process for rapidly developing effective DHF therapies. Through network pharmacology modeling, several FDA approved medications have already been researched for various viral outbreaks, by analyzing the interactions between virus-host gene interactions and therapeutic targets in the human genome network, a total of 45 repurposable medicines were discovered. Hub network analysis of host virus drugs association hypothesized that aspirin, captopril, rilonacept are efficient in the treatment of DHF, and gene enrichment analysis supports the findings. The human interactive contains the genes $PTGS_2$, ACE, and F_2, documented to have a role in the pathogenesis of disease progression of DHF, and our analysis of most of

the drugs targeting these genes. As a result, genes targeting medications play a significant part in limiting the condition's advancement.

Keywords: Dengue hemorrhagic fever; Drug reprofiling; Network pharmacology; Network medicine

Introduction

Dengue fever, also known as "break bone fever," is characterized by an acute prevalence of severe fever three to fourteen days after being bitten by an infected mosquito. migraine, retro-orbital pain, myalgia's, muscle aches, hemolytic anemia signs, rash, and a low white blood cell count are only a few of the symptoms [1]. Dengue Hemorrhagic Fever (DHF), a severe and sometimes fatal manifestation of the disease, affects certain dengue fever patients. The patient may acquire warning signs of serious disease about the period the fever began to diminish (typically 3–7 days following symptom onset). Severe abdominal discomfort, continuous vomiting, a significant change in temperature (from fever to hypothermia), hemorrhagic manifestations, or a change in mental status are indeed warning indicators (irritability, confusion, or obtundation). Restlessness, chilly clammy skin, a rapid weak pulse, and a narrowing of the pulse pressure (systolic blood pressure diastolic blood pressure) are all early indications of shock. Patients with dengue fever should be recommended to return to the hospital if any of these symptoms appear [2].

According to one estimate, 390 million dengue virus infections occur each year (95 percent credible interval 284–528 million), with 96 million (67–136 million) showing clinical symptoms (of any severity) [3]. According to dengue, 3.9 billion individuals are at risk of contracting the virus. Although there is a risk of infection in 129 nations, Asia bears 70% of the real burden. Over the last two decades, the number of dengue cases reported to WHO has increased by more than 8 times, from 505,430 cases in 2000 to over 2.4 million in 2010, and 5.2 million in 2019. Between 2000 and 2015, the number of deaths reported grew from 960 to 2032. This worrying rise in case numbers can be explained in part by a shift in national practices for recording and reporting dengue fever to health ministries and the World Health Organization. However, it also symbolizes the government's acknowledgment of the problem, and hence the need to disclose the prevalence of dengue fever 4As a result, while the complete global burden of the disease remains unknown, the observed growth only takes us closer to a more precise estimate of the full extent of the burden.

Dengue fever increased in Bangladesh, Brazil, the Cook Islands, Ecuador, India, Indonesia, the Maldives, Mauritania, Mayotte (Fr), Nepal, Singapore, Sri Lanka, Sudan, Thailand, Timor-Leste, and Yemen in 2020. Dengue fever is still a problem in Brazil, the Cook Islands, Colombia, Fiji, Kenya, Paraguay, Peru, and Reunion Island in 20215. The COVID-19 epidemic is putting enormous strain on healthcare and management systems all across the world. During this critical period, WHO has stressed the significance of maintaining efforts to prevent, identify, and treat vector-borne diseases such as dengue fever and other arboviral infections, as case numbers rise in various countries, putting urban people at risk for both diseases [4-6].

Recent systems biology developments suggest a unique testable hypothesis for systematic drug repositioning [7,8]. The time spent on R and D is greatly decreased when compared to traditional drug development programs. The typical strategy takes 10-16 years to develop a new treatment. A medication repositioning plan costs $1.6 billion to create, but a typical strategy costs $12 billion. The identification of

new targets and illness proteins has been made possible by rapid advances in genomic, proteomic, structural, functional, and systems investigations of existing targets and other disease proteins. In this study, we provide an embedded medicine platform that uses a network based method to quantify the association of DHF with human host interaction, and then we examine the efficacy of existing FDA approved medications as potential repurposable associations with DHF host genes. To discover and prioritize existing pharmacological targets in the DHF pathway, FDA approved medications are chosen from a clinical registry database.

Materials and Methods

Building the dengue hemorrhagic fever human interactive

Based on our literature similarity searches and database similarity searches found out more than 588 dengue hemorrhagic targeting human (host) genes based similarity hit to score 50 we sort out 5 host interacting dengue hemorrhagic fever genes reported experimental evidence for interactions between human proteins and dengue virus proteins based on high throughput yeast two hybrid screening methods Recently, Dey and Mukhopadhyay reported the development of denvInt, a database of manually curated experimental data of dengue protein and host protein interactions. We merged the data of published references from denvInt and used it in our analysis along with the dengue host interactive data from the recent investigations [9-11].

Human (host) gene dengue hemorrhagic fever gene interactive

The key host genes involved in dengue hemorrhagic fever were identified from the gene card database using the search terms “dengue hemorrhagic fever; dengue hemorrhagic fever interacting human genes”. Gene card is a searchable, integrative database that provides comprehensive, user friendly information on all annotated and predicted human genes. The knowledge base automatically integrates gene centric data from ~150 web sources, including genomic, transcriptomic, proteomic, genetic, clinical and functional information as of January 13, 2022 gene card comprises 326,787 genes are available in which 18,870 disease genes and 500 hot genes [12].The functions genes identified from gene card and related literature were collected and presented in supplementary file 1. The PPI network was built with cytoscape 3.9.0 v and Gephi 0.9.2 v 13 software.

Drug targets (human genes) interactive

We collect 87 FDA approved antiviral and anti-dengue hemorrhagic fever drugs from the Therapeutic Target Database (TTD) compare them with the results of the drug bank database and identified drug targets and formulated them as a dataset its available in supplementary file 1. We visualized it using cytoscape [13-16]. Nodes in networks represent antiviral drugs or anti-dengue hemorrhagic fever drugs and the nodes of the network represent drugs targeting human genes [17].

Building the drug to human interactive

A network pharmacological based host dengue hemorrhagic fever-antiviral-anti dengue hemorrhagic fever drugs interactive was constructed by assembling the host dengue hemorrhagic fever interacted proteins

with or without antiviral, anti-dengue hemorrhagic fever drugs. The PPI network was built with Gephi 0.9.2 v and cytoscape 3.9.0 v software. Each node in the constructed PPI network indicates a host gene and an edge indicates an interacting drug target [18].

Network hub gene identification

Highly connected nodes (hubs) in biological networks are topologically important to the structure of the network and have also been shown to be preferentially associated with a range of phenotypes of interest. Hub genes can be identified using the Contextual Hub Analysis Tool (CHAT) plug-in cytoscape 3.9.0 v which enables users to easily construct and visualize a network of interactions from a gene list of interest [19].

Network betweenness centrality analysis

Betweenness is a centrality measure of a vertex within a network; vertices that have a high probability to occur on a randomly chosen shortest path between two randomly chosen vertices have a high betweenness. The betweenness of a vertex α in a graph G: =(A,B) with A vertices and B edges [20]. For each pair of vertices (s,l), compute the shortest paths between them, For each pair of vertices (s,l), determine the fraction of shortest paths that pass through the vertex in question (here, vertex A). Sum this fraction over all pairs of vertices (sl). The degree Cb of node b is calculated as follows.

$$C_b(A) = \sum_{s \neq A \neq l \in A} \frac{\sigma_{sl}(A)}{\sigma_{sl}}$$

Were, (A) is the number of shortest paths from s to l that pass through a vertex A [21].

In a connected graph, the normalized closeness centrality (or closeness) of a node is the average length of the shortest path between the node and all other nodes in the graph [22]. Thus, the more central a node is, the closer it is to all other nodes.

$$C_a = \frac{1}{\sum_b d(a,b)}$$

Were d (a,b) being the distance between vertices a and b

Functional enrichment analysis for genes and drugs

Functional enrichment analysis is a method to determine classes of genes or drugs that are over-represented in a large group of genes or drugs and may have relations with disease phenotypes. This approach uses statistical methods to determine significantly enriched groups of genes [23]. The biological relevance and functional pathways of our datasets were revealed by enriching the semantic similarities of the pathway, tissue. All functional enrichment analyses were performed using the enrichment platform as additional evidence for drug repurposing. The enrich is a comprehensive gene enrichment analysis platform that comprises 382,208 terms from 192 libraries. The combined score is described as

c=log (p).z

Where c=the combined score, p=Fisher exact test p-value, and z=z-score for deviation from expected rank.

Results

Human (Host) dengue hemorrhagic fever (viral) gene interactive

We constructed a host DHF interactive consisting of 59 interacting genes with 60 nodes and 59 edges

(Supplementary Figure 1a). Based on Kegg pathway enrichment analysis indicates genes involved in the AGE-RAGE signaling pathway in diabetic complications enriched (P=3.01E-32) the most which indicate patients with DHF condition have a higher chance of poor blood sugar management while in the pathogenesis, AGE/RAGE signaling has been shown to increase oxidative stress to promote diabetes mediated vascular calcification through activation of Nox-1 and decreased expression of SOD-1 and chagas disease (P=4.65E-32) and influenza A pathways are typically enriched (P=6.17E-31) [24]. Compare to Kegg pathway analysis reactive pathway analysis indicates immune system (P=3.93E-28) and cytokine signaling in immune system (P=7.06E-27) are enriched which indicates DHF hijack human immune system associated gene pathway the most, gene set in which immune system (1.12E-61) bronchoalveolar lavage (2.85E-50) tissues are enriched the most (Supplementary Figure 1b).

Host-viral-antiviral drugs target interactive

A host-DHF-antiviral drug interactive was built with 298 nodes and 370 edges from 237 interacting genes (Supplementary Figure 2a). based on Kegg pathway genes enrichment analysis reactive ligand receptor interaction (P=3.22E-45) *i.e.,* collection of genes associated with intracellular and extracellular signaling pathways on the plasma membrane and MAPK pathways (P=9.57E-45) that relay, amplify and integrate signals from a diverse range of stimuli and elicit an appropriate physiological response including cellular proliferation, differentiation, development, inflammatory responses and apoptosis in mammalian cells enriched the most upon antiviral drug administration (Supplementary Figure 2b). According to reactive pathway analysis indicate Phase to plateau phase (P=2.85E-34) that sustains cardiac action potential muscle contraction and transmission across chemical synapses (neurotransmitters) (P=6.03E-34) pathway genes enriches and adult (P=2.52E-69), immune system (P=1.77E-49) tissue types expressed more on antiviral drug administration on HDF according to our enrichment analysis [25,26].

Host-viral-anti-dengue hemorrhagic fever drugs target interactive

A host-DHF interactive anti-dengue hemorrhagic fever drugs interactive was built with 558 nodes and 861 edges from 419 interacting genes (Supplementary Figure 3a). Retroactive ligand receptor interaction (P=3.37E-75), cAMP signaling pathway (P=2.29E-54) also known as the adenylyl cyclase pathway, is a G protein coupled receptor-triggered signaling cascade used in cell communication are the most enriched gene pathway respectively according to Kegg pathway analysis (Supplementary Figure 3b). Amine ligand binding receptors (1.76E-47) act as neurotransmitters in humans, signal transduction (P=1.40E-46) involves the binding of extracellular signaling molecules and ligands to receptors located on the cell surface are highly enriched. Adult (P=1.74E-59), immune system (P=3.35E-54) are the most prominent tissue type during anti-dengue hemorrhagic fever drugs administration for COVID-19 patients.

Host-viral-antiviral-anti-dengue hemorrhagic fever drugs target interactive

Based on all the interatomic data sets, we combine all the data sets to frame a network-based drug profiling approach to testing the robustness with which it involves network contains 717 nodes and 1175 edges from 487 interacting genes (Figure 1).

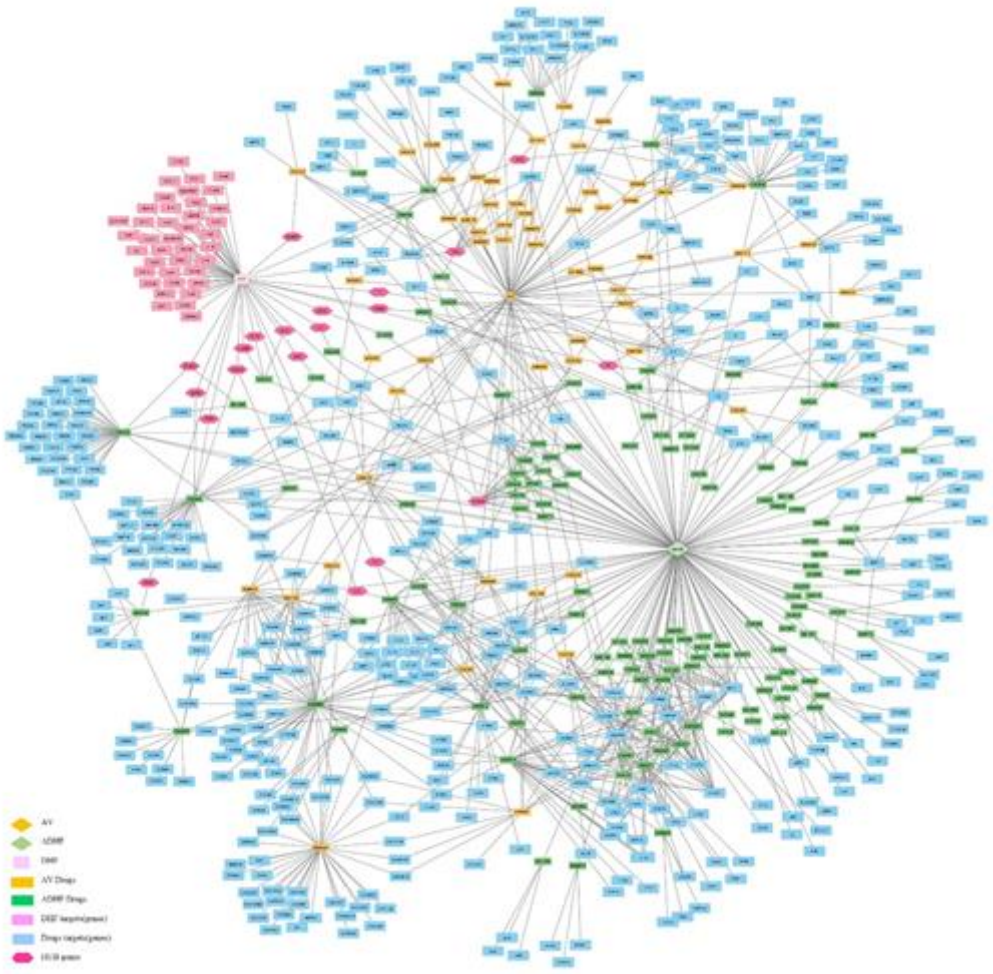

Figure 1: Human-DHF-AVD-ADHFD interaction network.

Gene functional enrichment analysis of the Kegg pathway reveals that gene sets involved in neurotransmitters pathways (P=1.13E-84) and calcium signaling pathway (P=1.78E-66) are highly enriched as similar as in previous drug related host virus interactive in human's it also provides a stable outcome when a combined drug administration (antiviral, AHDFD) is employed during systemic DHF patients (Figure 2). The majority of a gene set is enriched in adult (P=1.53E-77), immune system (P=3.07E-63) tissues. Genes related to signal transduction (P=6.76E-56), signaling by GPCR (P=1.96E-49) are prevalent reactive pathways enriched in DHF patients with combined drug medication.

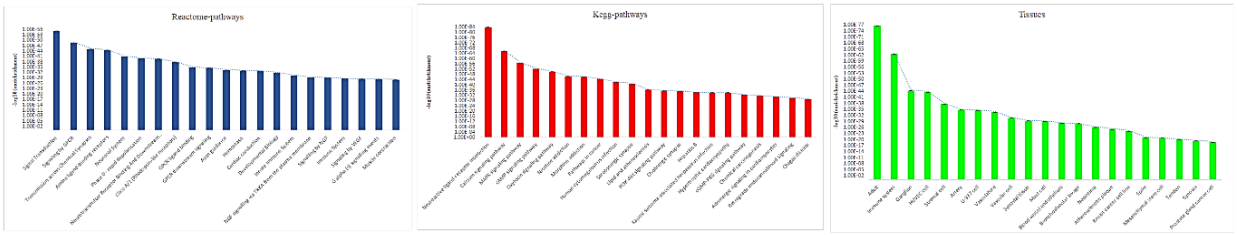

Figure 2: Enrichment analysis of human-DHF-AVD-ADHFD.

Network based drug repurposing based on hub gene analysis

We predicted a hub gene module containing 20 interacting genes (66 nodes and 113 edges) from the above interactive of the host-virus-drugs systems framework (Figure 3).

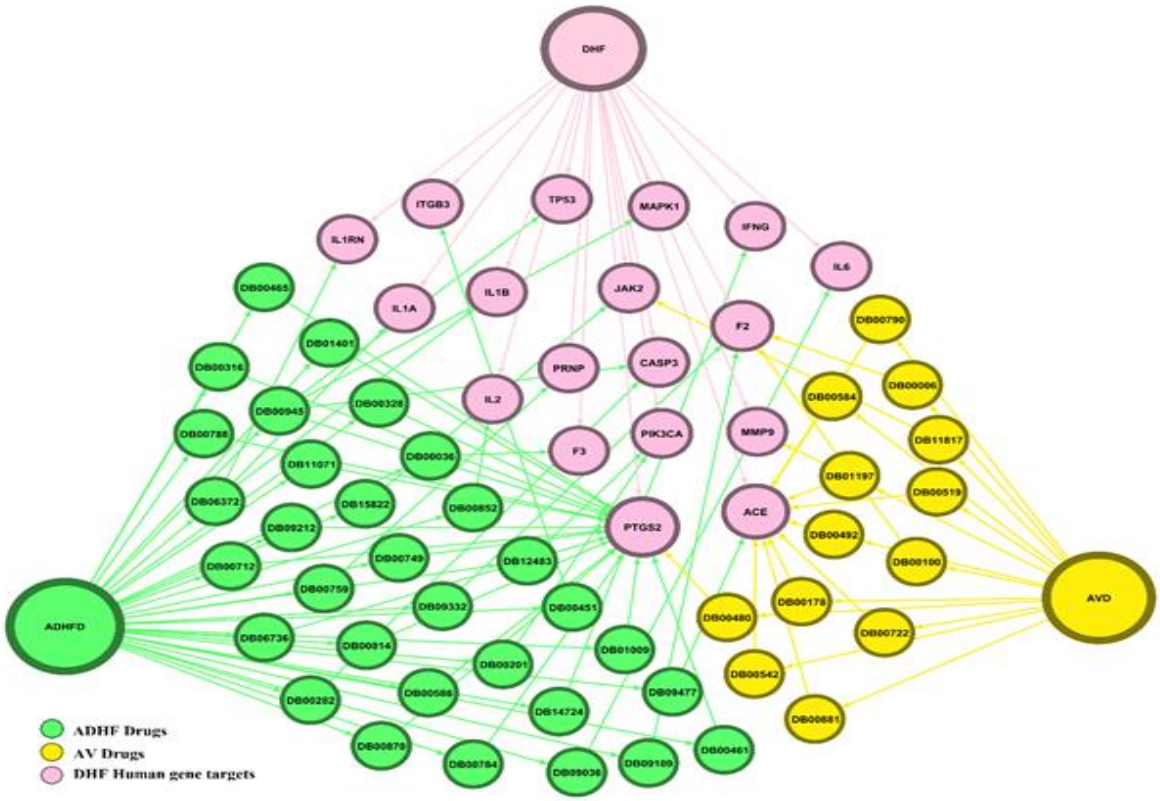

Figure 3: Representation of human interacting-DHF-AVD-ADHFD hub network.

A total of 45 drugs are repurposed from the hub gene module in which 13 antiviral drugs and 32 anti-dengue hemorrhagic fever drugs. From the hub gene-drug association network we find out that 3 major drugs bind efficiently with DHF targeting human genes, aspirin, captopril, and rilonacept is efficient FDA approved drugs that can be used in the treatment of DHF (Figure 4).

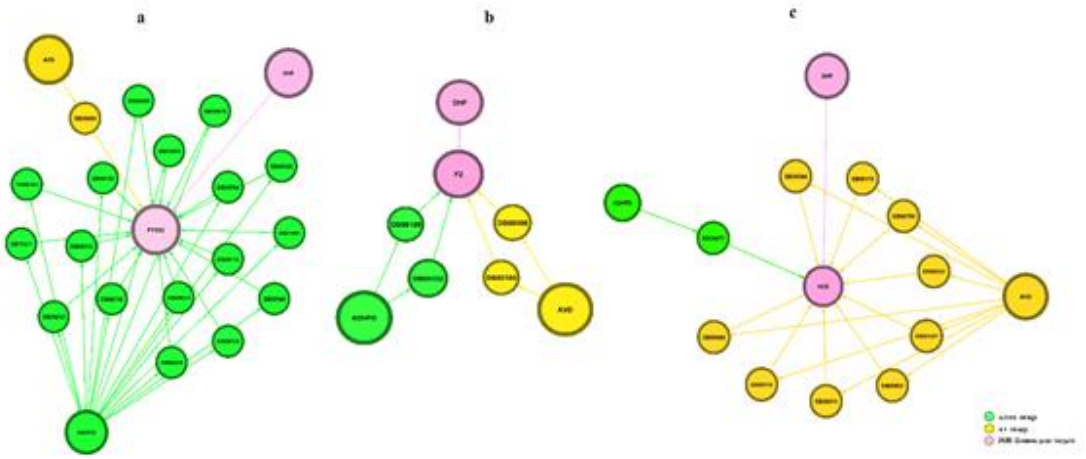

Figure 4: a) PTGS2; b) F2; c) ACE genes interactions in hub-network.

We identified 18 $PTGS_2$ genes, 10 ACE, 4 F_2, targeting drugs in hub genes in the network. Interestingly 18 out of 17 $PTGS_2$ targeting drugs are ADHFD and 10 out of 9 ACE targeting genes are antiviral drugs in property, moreover, F_2 targeting drugs are equal numbers *i.e.,* 2 AVD and 2 ADHFD (Figure 5).

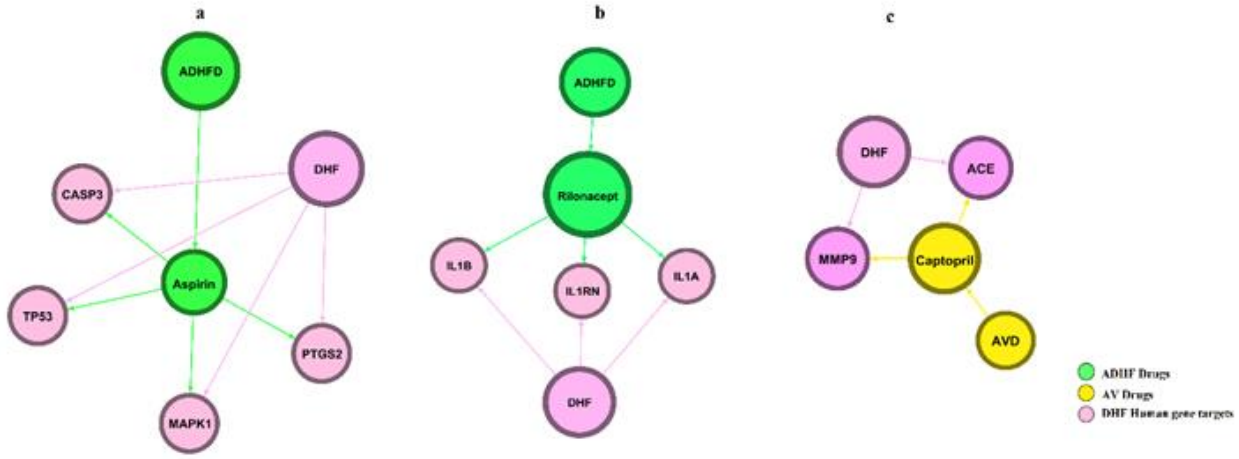

Figure 5: Repurposable drugs a) Aspirin; b) Rilonacept; c) Captopril identified through hub-network analysis.

Gene enrichment analysis shows that the hub gene module is highly enriched in tissues associated with the immune system (P=7.29E-24), HUVEC cell (P=1.83E-20) this group of tissues act as an anticoagulant barrier between the vessel wall and blood, Kegg analysis shows that genes associated with cancer (P=1.13E-14), AGE-RAGE signaling pathway in diabetic complications (P=3.52E-14) which indicate that DHF patients with diabetes and cancer are risk of higher pathogenicity. Reactive pathway gene enrichment gives the evidence of immune systems associated pathways *i.e.,* signaling by Interleukins (2.04E-14), cytokine signaling in immune system (7.12E-14) enrich the most (Figure 6).

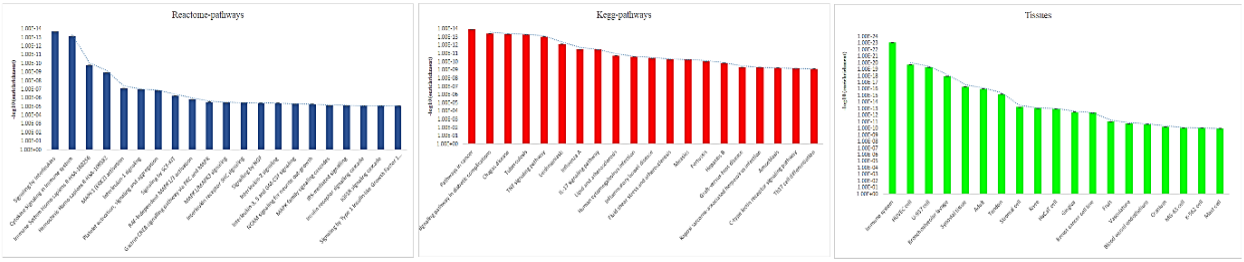

Figure 6: Functional hub-gene enrichment analysis.

Discussion

Functional enrichment analysis of drugs based on hub gene prediction

A total of 45 repurposable drugs were enriched for hub drug mechanism, gene expression of specific systems, and side effects (Figure 7). It shows that flurbiprofen, mefenamic acid, acetylsalicylic acid, indomethacin, naproxen, ketoprofen, acetaminophen, ketorolac, aceclofenac, lenalidomide, diclofenac, suprofen, loxoprofen, and nabumetone are $PTGS_2$ targeting the hub gene module dyspnoea, shock, renal failure, nervousness, tension are prominent side effects of these drugs. Prostaglandin metabolic process (P=0.000162675), regulation of wnt signaling pathway (P=0.000307855) are prominent upregulated gene expression pathways during the above drug administration.

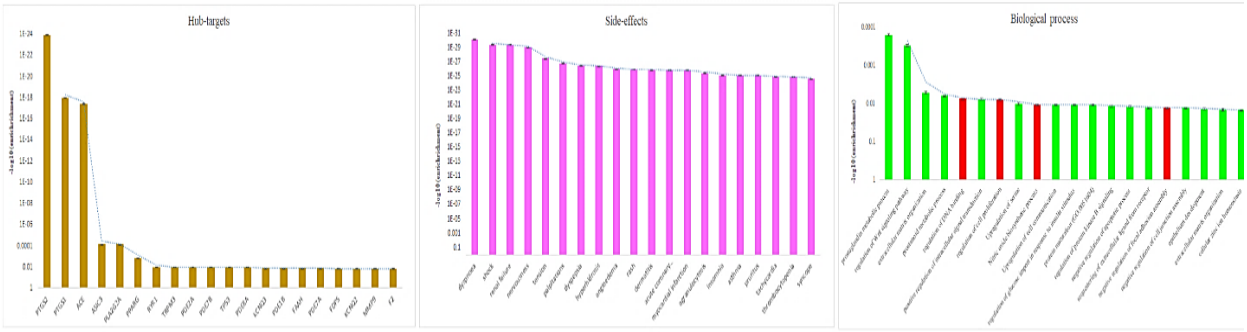

Figure 7: Functional hub-drug enrichment analysis.

Conclusion

We systematically study the association of the dengue viral interaction with the human genome through network based association analysis. It is hypothesized that a host protein that functionally associates with this virus is localized in the corresponding sub-network within the comprehensive human interactive network. The host dependency factors mediating virus infection and effective molecular targets should be identified for developing broad spectrum antiviral drugs and ADHFD

for DHF. In our network based analysis, we identified 45 repurposable drug candidates against DHF targeting the human gene in which 13 antiviral and 32 ADFHD that targeting 20 human genes; the most prevalent side effect identified in repurposed drug enrichment was dyspnoea and shock. $PTGS_2$, F_2, and ACE genes are the highly targeted repurposed drugs, and it already reported the pathogenicity of $PTGS_2$/COX-2 gene pathways in the progression of DHF. Most importantly $PTGS_2$ gene has a direct relationship with severe dengue happens when your blood vessels become damaged and leaky. And the number of clot forming cells (platelets) in your bloodstream drops. This can lead to shock, internal bleeding, organ failure and even death inhibiting this helps further prevent heart disease and better management of dengue hemorrhagic fever. For that, we sort out several effective targeting drugs based on our repurposing approach they are aceclofenac, acetaminophen, aspirin, choline magnesium trisalicylate, diclofenac, etodolac, epinephrine, indomethacin, ketoprofen, ketorolac, loxoprofen, mefenamic acid, meloxicam, nabumetone, naproxen, phenyl salicylate, suprofen, lenalidomide, enrichment analysis evidently emphasis most of the pathways of the immune system are enriched the most and adult and immune system associated tissues are associated with viral and drug response enriched throughout the study. This network based analysis hypothesized that 3 drugs have repurposable properties are aspirin, captopril, rilonacept further studies are needed to prove its efficiencies in DHF patient treatment.

Declaration of Conflicting Interests

Authors have no Conflicting Interests.

Funding Acknowledgement

Acknowledgement to “Ministry of Higher Education Malaysia for Fundamental Research Grant Scheme with Project Code: FRGS/1/2020/SKK0/USM/03/16

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