Study on the Biological Basis of Hypertension and Syndrome with Liver-Fire Hyperactivity Based on Data Mining Technology

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Abstract

Objective: To construct gene co-occurrence network of hypertension and liver-fire hyperactivity syndrome, to investigate the biological basis of hypertension and liver-fire hyperactivity syndrome and the characteristics of the molecular network from gene level. Materials and Methods: Applying GenCLip 2.0 online platform to retrieve the up-to-date literature referred to essential hypertension from PubMed database, cluster the abnormal expression of essential hypertension-related genes and analyze their function, combining Kyoto encyclopedia of genes and genomes-pathway analysis to investigate the closely related genes and the signaling molecules. Based on the genes closely related to hypertension, standard diagnostic symptoms of liver-fire hyperactivity were used as keywords to conduct hypertension-liver-fire hyperactivity-related gene cluster analysis. Results: The top 1000 genes of essential hypertension were retrieved from GenCLip 2.0 online platform, which mainly clustered in the regulation of ambulatory blood pressure, regulation of renin-angiotensin-aldosterone system (RAAS), and sympathetic nervous system activity, as well as endothelial dysfunction; the closely related genes of hypertension with liver-fire hyperactivity are related to RAAS, gene REN, angiotensin converting enzyme, angiotensinogen, and cytochrome P450 family CYP2D6. Conclusion: A combination of literature mining and data mining can construct the gene network of hypertension and the syndrome-related genes, which provides a new method for the study of the biological basis of hypertension from the genetic level.

Keywords: Biological basis, data mining, essential hypertension, gene chip, liver-fire hyperactivity syndrome

Introduction

The current research on the biological basis of disease and syndrome meets many difficulties, such as using gene clip detection methods to analyze the differentially expressed genes (DEGs) will cost a lot and consuming much time if verified one by one, since there are a large number of DEGs.[1] Applying data mining and literature mining methods to conduct disease-syndrome-related gene network has significant value in explaining the biological basis of disease and syndrome.[2] Liver-fire hyperactivity syndrome is one of the most common syndromes of essential hypertension.[3] Thus, this research conducts a preliminary study on the biological basis of hypertension and liver-fire hyperactivity from the genetic level.

Materials and Methods

Literature resource

All the literatures were extracted from PubMed full-text database.

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Essential hypertension-related genes and keywords extraction

All literatures related to hypertension were retrieved from PubMed database by GenCLip 2.0 online platform. Extract the top-100 genes related to essential hypertension to form hypertension closely related gene list. Extract keywords from the retrieved literature related to hypertension automatically.

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then check or delete keywords that are not related to or meaningless. Referring to the Chinese medicine clinical guidelines for hypertension of hyperactivity of liver-fire syndrome, add the corresponding names of the symptoms as keywords in traditional Chinese medicine (TCM) and Western medicine that is closely related to the liver-fire hyperactivity syndrome.

**Gene cluster analysis and network construction**

Conduct clustering analysis of the top-100 genes related to essential hypertension based on the keywords. Apply GenCLip 2.0 to explore the related gene regulating signal molecules and construct the molecular network in hypertension with hyperactivity of liver-fire syndrome.

**Kyoto encyclopedia of genes and genomes-pathway analysis**

Apply Functional Annotation Tool-DAVID Bioinformatics Resources 6.7, NIAID/NIH to conduct Kyoto encyclopedia of genes and genomes (KEGG)-pathway analysis.

**Results**

**Essential hypertension related-genes**

The top 100 genes of essential hypertension retrieved from GenCLip 2.0 online platform are as shown in Table 1.

**Results of gene-function clustering analysis**

The clustering analysis results of essential hypertension-related genes are as follows [Figure 1]: clustered in the regulation of ambulatory blood pressure (circadian rhythm), regulation of rennin-angiotensin-aldosterone system (RAAS), and sympathetic nervous system activity, as well as endothelial dysfunction.

**Results of gene co-occurrence network**

The gene co-occurrence network of essential hypertension is shown in Figures 2 and 3. The co-genes and co-cite numbers of essential hypertension related-genes are demonstrated in Table 2.

**Results of Kyoto encyclopedia of genes and genomes-pathway analysis**

KEGG-pathway analysis of the closely related top 100 genes is shown in Table 3.

The clustering results of the rennin-angiotensin system, aldosterone-regulated sodium reabsorption, cytokine-cytokine-receptor interaction calcium signaling pathway, and Nucleotide binding oligomerization domain (NOD)-like receptor signaling pathway is shown in Figure 4.

**Results of genes related to hypertension with liver-fire hyperactivity syndrome**

Referring to the Chinese medicine clinical guidelines for hypertension of hyperactivity of liver-fire syndrome, add the corresponding names of the symptoms as keywords in TCM and Western medicine that is closely related to the liver-fire hyperactivity syndrome [Table 4].

The study found that the symptoms of liver-fire hyperactivity, such as dry mouth closely related genes of RAAS pathway, Renin (REN), angiotensin-converting enzyme (ACE), angiotensinogen (AGT), and cytochrome P450 family CYP2D6 Figure 5, which also provide clues from the genetic level to find the target in the treatment of hypertension with different syndromes of medicine.

**Discussion**

The biological basis of the syndrome has been the key point and difficulty in the study of TCM. Data mining methods, which
are based on feature selection, are better fit for investigating the biological basis of TCM syndrome. The literature mining software GenCLip2.0, invented by Huang Zhongxi, associate professor of Southern Medical University, which can cluster the DEGs, as well as conduct special functional gene network. Inserting the disease-related gene into the software, it will not only show the name of the gene and ID but can also show all the literature relevant to the function of the genes annotation and the abstract of all the literature from Pub Med gene library. It is very convenient for the researcher to check the information. At the same time, researchers can add or combine keywords according to their own research to mining the relationship of the genes. Finally to obtain the signal pathway or network based on the genes to be analyzed and specified keywords. Since the software is updated in real time, so the relationship of genes and keywords mining by the software is also constantly updated. The genetic mechanism, network, and signal pathway are the latest. Zhu Wenhua[9] used GenCLip2.0 online tools to mine literature related to DEGs. Finally, the gene ontology and path enrichment analysis of DEGS in the literature were carried out, and the molecular mechanism of the influence of intestinal flora on intestinal health was discussed. Liu Jing[10] identified important modules in the network of potential molecular targets for coronary heart disease and analyzed the pivotal genes in the module through GenCLiP2.0 tools to identify important sub-pathways. The key genes and biological pathways of prostate epithelial cell response after low-dose cadmium exposure were identified by Liu Qiling[11] bioinformatics analysis using Genclip and other software.

Pub Med database is the most authoritative clinical medical literature database in the world, and it is also the most frequently used database for medical users to obtain foreign medical information. KEGG analyzes the genome and the depth information of functional gene, combined by intracellular biological processes and the existing computer information standardization of gene function, to analyze the gene function systematically. Combination of literature mining and data mining can construct the gene network of hypertension and the syndrome related genes, which provides a new method.
for the study of the biological basis of hypertension from the genetic level.\textsuperscript{[13]}

The currently known candidate genes of essential hypertension involve in many functions, including the sympathetic nervous system, the RAAS, atrial natriuretic peptide, the kallikrein-kinin system, growth factors and hormones, cytoskeletal proteins and adhesion molecules, intracellular messenger, lipid metabolism, glucose metabolism, ion channel, or transporter.\textsuperscript{[14]} By applying Gen CLiP 2.0 gene mining software and KEGG-pathway analysis, this research clustered the function of the top 100 genes of Essential hypertension (EH), constructed a network of essential hypertension, and found that REN, ACE, AGT, tumor necrosis factor, transforming growth factor beta-1, and arginine vasopessin (AVP) genes were the most closely related genes. Clustering as circadian rhythm of blood pressure regulation and dynamic changes of blood pressure, hormone secretion, vasoactive substances and glucose tolerance, RAAS, sympathetic nervous system, and blood vessel endothelial function regulation pathway.

In this study, hypertension with liver-fire hyperactivity syndrome was taken as an example to explore the correlation between syndromes and gene. The study found that dry mouth...
symptoms closely related genes of RAAS pathway key genes REN, ACE, AGT, and cytochrome P450 family CYP2D6, which also provide some clues from the genetic level to find the target in the treatment of hypertension of different syndromes of medicine. This study uses the existing scientific research results from the literature summary, preliminary study of molecular basis of disease and syndromes of hypertension from genes and signaling pathways, to provide a reference for clinical research on hypertension and TCM syndrome. However, due to the limitation of quantity and quality of TCM literature research in hypertension syndrome, further research combining with literature and the results of experimental and clinical need to be conducted to explain the biological basis of TCM syndrome.

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**Table 4: The corresponding names of the symptoms of liver-fire hyperactivity**

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptoms</th>
</tr>
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<tbody>
<tr>
<td>Hyperactivity of liver fire</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Liver-fire excess</td>
<td>Headache, cranialgia, cephalgia</td>
</tr>
<tr>
<td>Liver-fire hyperactivity</td>
<td>Dysphoria, restlessness, irritability</td>
</tr>
<tr>
<td></td>
<td>Flushed face</td>
</tr>
<tr>
<td></td>
<td>Conjunctival congestion</td>
</tr>
<tr>
<td></td>
<td>Dry mouth</td>
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<td></td>
<td>Bitter taste</td>
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<tr>
<td></td>
<td>Constipation</td>
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<td></td>
<td>Yellow urine</td>
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<tr>
<td></td>
<td>Red tongue, yellow tongue fur</td>
</tr>
<tr>
<td></td>
<td>Wiry rapid pulse</td>
</tr>
</tbody>
</table>

**Figure 4: Clustering results of kyoto encyclopedia of genes and genomes-pathway**

**Figure 5: Clustering result of genes related to hypertension with liver-fire hyperactivity**

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Nil.

**Conflicts of interest**

There are no conflicts of interest.

**References**