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A pathway-based network analysis of hypertension-related genes

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HIGHLIGHTS

- A network of hypertension-related genes is proposed based on biological pathways.
- Statistical and topological characteristics of the gene network are analyzed.
- Seven key hub genes of hypertension are determined through integrated centrality.
- The modular structure analysis can facilitate the exploration of drug targets.
- The network approach provides another perspective to explore disease pathogenesis.

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ABSTRACT

Complex network approach has become an effective way to describe interrelationships among large amounts of biological data, which is especially useful in finding core functions and global behavior of biological systems. Hypertension is a complex disease caused by many reasons including genetic, physiological, psychological and even social factors. In this paper, based on the information of biological pathways, we construct a network model of hypertension-related genes to explore the interrelationship between genes. Statistical and topological characteristics show that the network has the small-world but not scale-free property, and exhibits a modular structure, revealing compact and complex connections among these genes. By the threshold of integrated centrality larger than 0.71, seven key hub genes are found: Jun, Rps6kb1, Cycs, Creb312, Cdk4, Actg1 and RT1-Da. These genes should play an important role in hypertension, suggesting that the treatment of hypertension should focus on the combination of drugs on multiple genes.

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1. Introduction

The study of complex systems clearly shows that the global behavior of systems is determined by their structure rather than by the properties of their individual parts. The complex network approach has become a powerful tool for studying complex systems, and the global properties of systems are usually studied by abstracting individual elements of systems into nodes and reducing interactions between elements to edges between nodes [1–5]. Such an approach has been widely applied to understanding gene functions in biological and medical research [6–10].

Essential hypertension, which accounts for about 90%–95% of all cases of hypertension [11], is a disease caused by long-term interaction between genetic and environmental factors, and salt is one of the important environmental factors [12]. The blood pressure response to salt loading or salt restriction is heterogeneous among individuals, which is known as salt sensitivity [13–15]. Salt sensitivity is the genetic susceptibility of individual blood pressure response to salt, and is an intermediate phenotype of essential hypertension [16,17]. The people who suffer the salt-sensitive (SS) hypertension account for about 50% of hypertensive patients [15]. Although the clinical research and treatment of hypertension have improved dramatically [18–20], its molecular mechanisms and pathologies involved are still difficult to ascertain.

Many omic data have been obtained and become available through advanced high-throughput technologies, which provide the basis for studying the relationship of biological data by network approach [7,10]. Various biomolecular networks have been constructed to discover essential functions and mechanisms of biological phenomena [6,8,9]. For instance, Censi et al. studied the gene regulatory networks induced in heart tissue by atrial fibrillation [21]. Demicheli and Coradini analyzed breast cancer behavior using gene regulatory networks [22]. Therefore, it is of significance to understand hypertension disease at system level using the complex network approach.

In our previous study [23], we constructed a hypertension-related gene co-expression network by focusing on the analysis of gene expression data (GED) [24] among the Dahl SS rat [25,26] and two consomic rat strains [27,28], where the 335 nodes are individual genes and the connections are derived from the expression correlations. This is a theoretical analysis based on GED to determine the key hub genes (nodes) and explore the relationship between these hub genes and hypertension. However, to get more biologically relevant information about hypertension, a pathway-based gene network should also be constructed using the actual biological correlations.

In the present work, we attempt to study the genes that are involved in SS hypertension based on the information of biological pathways. A biological pathway is a series of actions among molecules in a cell that leads to a certain product or a change in a cell [29,30]. Such a pathway can trigger the assembly of new molecules or turn genes on and off. Since biological pathways such as metabolic and signal transduction pathways can directly be viewed as interconnected processes of molecular species in the cell [29,30]; therefore, constructing a pathway-based gene network could help to disentangle the actual biological interactions between genes.

In this paper, we will construct the network model of hypertension-related genes according to whether these genes are involved in the same pathways in the KEGG[1] database. Network approach will be employed to investigate the possible relations between network structure and hypertension-related genes based on these data. Through calculating several statistical indices and analyzing topological characteristics of the network, we find that the pathway-based gene network exhibits the small-world but not scale-free property. Meanwhile, the network also exhibits a modular structure: the nodes of the network can be properly divided into groups within which the nodes are highly connected, but between which they are much less connected. The modular structure analysis can visualize the weak connections of the network, and thus help us to study drug targets of hypertension. The results from this paper and the analysis in Ref. [23] would complement each other.

The rest of this paper is organized as follows. In Section 2, we introduce the data source and construct the pathway-based gene network model of hypertension. In Section 3, we analyze the statistical and topological characteristics of the gene network. The modular structure of the network is presented in Section 4, while Section 5 presents summary and concluding remarks.

2. Data source and network construction

The Dahl SS rat, proposed by Dahl et al. in the early 1960s [25,26], is a widely used genetic model of human hypertension. The consomic rat strains, used as the normotensive control for the Dahl SS rat, are generated by substituting a chromosome or a part of a chromosome from a normal rat strain for the corresponding genomic region of the SS rat [24,27,28]. Previous research has shown that substitution of chromosome 13 or 18 can attenuate hypertension [31,24]. Our study will focus on the hypertension-related genes listed in Ref. [24] by analysis of biological pathways.

Let us consider an undirected network $G_H = (V_H, E_H)$, where $V_H = \{v_i\}$ $(i = 1, 2, \ldots, N)$ denotes the set of N nodes, and $E_H = \{v_i, v_j\}$ the set of edges or connections between nodes. We will use the following notation: $A_{ij} = 1$ indicates that there is an edge between nodes v_i and v_j; and $A_{ij} = 0$ otherwise. Our pathway-based gene network model is constructed in two steps.

[1] KEGG (Kyoto Encyclopedia of Genes and Genomes) website: http://www.kegg.jp/ or http://www.genome.jp/kegg/.

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