

Discover the Dehydration Response Genes in *Boea hygrometrica* Transcriptome Using Bayesian Network Approach

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Abstract: “Drying without dying” is an amazing feature in land plant evolution. *Boea hygrometrica* is an important resurrection plant model. The current genome and transcriptome analysis have revealed that some biological processes may contribute to its dehydration tolerance, but genes play pivotal roles in the dehydration response remains unclear. Bayesian network approach is a powerful tool for transcriptome data analysis and biological network reconstruction. In this work, by using the Bayesian network approach, we first reconstruct a gene regulation network with the *B. hygrometrica* transcriptome data. The network contains 1292 genes. Next, we defined the hub node genes in the network and focus on their functions in order to understand the response *B. hygrometrica* carried out under the dehydration stress. Finally, by an association analysis, we deduce the function of the unknown gene *Bhs126_021* which has a degree of 84 in the network. The data-driven strategy we applied in this work not only finds out the knowledge from the knowledge-driven strategy analysis, but also provides novel findings from the *B. hygrometrica* transcriptome. Our findings give insight of control genes in land plant under the dehydration stress. The data-driven strategy applied in this work can also efficiently analyze other similar transcriptome data sets.

Keywords: Dehydration Response Genes, *Boea hygrometrica*, Bayesian Network, Transcriptome Analysis

1. Introduction

Boea hygrometrica is a homiochlorophyllous dicot in Gesneriaceae that grows in rocky areas throughout most of China [1]. It is an important plant model for understanding responses to dehydration. In 2015, the draft genome of *B. hygrometrica* was sequenced. The genome size of *B. hygrometrica* is about 1.69 Gb. The genome encodes 23,250 genes. The dehydration-induced alteration in gene expression experiments discovered 9,888 differentially expressed genes (DEGs) [2]. Knowledge-based analysis of its transcriptome revealed three major clusters of genes involved in dehydration stress response. Cluster 1 primarily associated with photosynthesis. Cluster 2 was mainly of ABA metabolism and signaling, late embryogenesis abundant proteins (LEAs) and components of ROS protection and detoxification pathways. Cluster 3 primarily encoded proteins for nucleic acid

metabolism. However, knowledge-based analysis did not find the genes played key roles in *B. hygrometrica* under dehydration stress. The key controlling genes for the dehydration tolerance in *B. hygrometrica* remains unknown.

Bayesian network approach [3] is a promising tool for transcriptome data analysis [4-7] and biological network reconstruction [8-12]. Bayesian network approach is a kind of data-driven analysis method. It is independent of the known knowledge and could mine the novel knowledge merely based on the dataset itself.

To investigate the mechanisms of the dehydration tolerance in *B. hygrometrica*, in this work we reconstructed the *B. hygrometrica* gene regulatory network using Bayesian network approach, and discover pivotal control genes in *B. hygrometrica* against dehydration stress. The pipeline used in this work can also be converted to analyze other transcriptome data.

2. Data & Methods

2.1. Transcriptome Datasets

Genome-wide transcriptome dataset during dehydration in leaf tissues of *B. hygrometrica* was collected from Gene Expression Omnibus (GEO) database (<https://www.ncbi.nlm.nih.gov/geo/>), the accession numbers are GSE48671 and GSE66474.

In this work, we extracted the data of the 1292 two-fold differentially expressed genes to reconstruct the Bayesian network.

2.2. Reconstruction of *B. hygrometrica* Gene regulatory Network Using Bayesian Network Approach

Bayesian network is a probabilistic graphical model that represents a set of random variables and their conditional dependencies via a directed acyclic graph (DAG). It consists of two components: the first component is a directed acyclic graph; and the second component is a set of parameters that quantify the network [9]. A Bayesian network is defined as:

$$P_B = (X_1, \dots, X_n) = \prod_{i=1}^n P_B(X_i | pa(X_i))$$

Where:

X_i denotes each variable in DAG, $pa(X_i)$ denotes all parent

nodes of X_i .

In this study, we used the R package bnlearn (<http://cran.r-project.org/>) to learn the Bayesian network structure.

2.3. Visualization of the Gene Regulatory Network

We use Cytoscape 2.8.3 (<http://www.cytoscape.org/>) software to visualize the gene regulatory network [13].

3. Result and Discussions

3.1. Gene Regulatory Network of *B. hygrometrica*

First, we reconstructed the *B. hygrometrica* gene regulatory network using Bayesian network approach. The gene regulatory network includes 1292 nodes and 8969 edges (Figure 1). The distribution of the node degree showed that only 114 nodes (less than 10%) have a degree greater than 25 (Figure 2). The distribution follows the power law. The result suggested that *B. hygrometrica* gene regulatory network is a scale-free network. The scale-free networks are remarkably resistant to accidental failures [14]. Since the hub nodes (i.e. nodes having high degree of connectivity) in a scale-free network dominate the overall connectivity of the network, these hub nodes play important roles for maintaining the stability of the network [15].

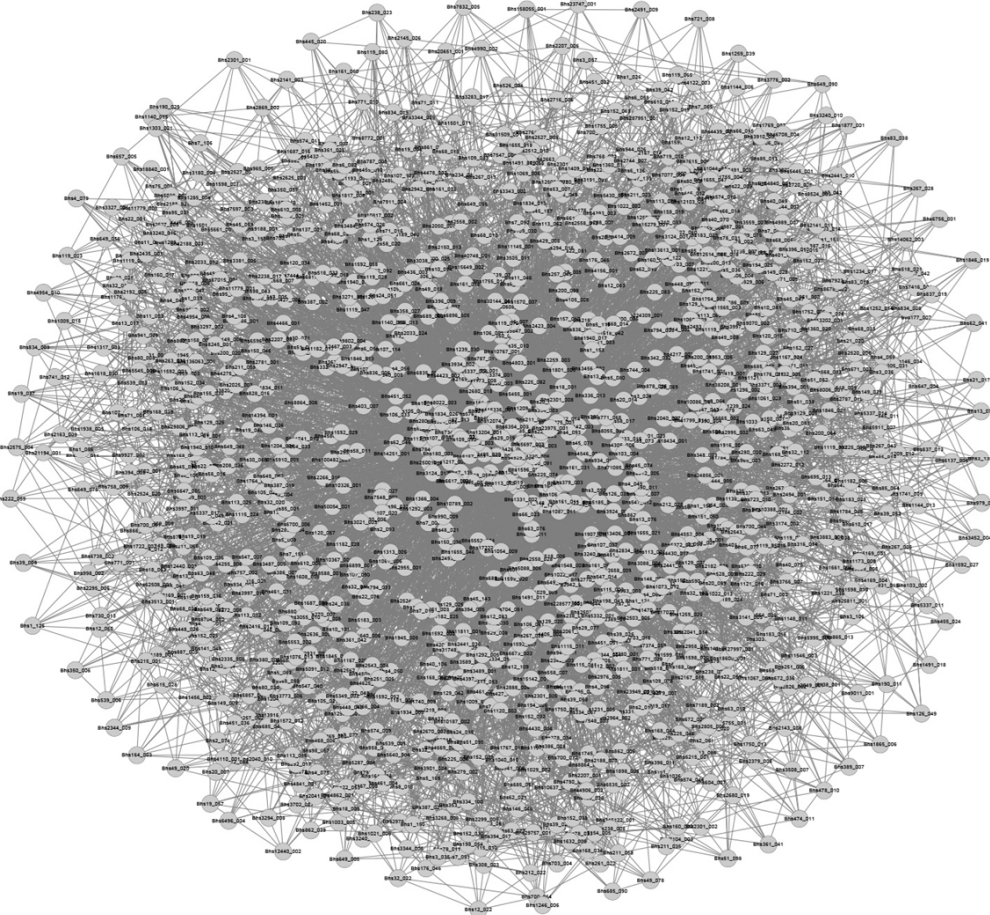


Figure 1. Gene regulatory network of *B. hygrometrica*.

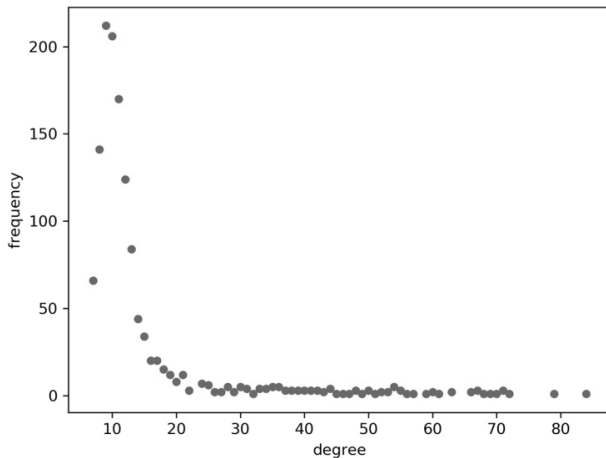


Figure 2. The distribution of node degrees.

3.2. Dehydration Response Genes in *B. hygrometrica*

After reconstructing the gene regulatory network, we focused our analysis on the hub nodes in *B. hygrometrica*, and expected to find out the key controlling genes involved in the dehydration tolerance in *B. hygrometrica*.

In this work, we defined the hub node genes as the genes with the degree equal to or greater than 40. We found 58 hub nodes in the *B. hygrometrica* gene regulatory network. Table 1 shows the 18 hub nodes with degree above 60. Hub nodes play pivotal role in a network. Therefore, these hub node genes are of key genes involved in the dehydration response in *B.*

hygrometrica.

Previous study has shown that three clusters of genes involved in dehydration response [2]. The first cluster is associated with photosynthesis. In this work, by using the Bayesian network approach, we independently discovery that the hub node gene *Bhs3_009* with a degree of 79 associates with photosynthesis (Table 1). The second cluster is mainly of ABA metabolism and signaling. In the gene regulatory network, we discovered two hub node genes *Bhs6354_003* (52) and *Bhs109_092* (43) (Numbers after each gene is the degree of the gene in the network, the same here after) participate in the abscisic acid (ABA) mediated signaling pathway (Table 1). The third cluster encoded proteins for nucleic acid metabolism. In the gene regulatory network we discovered four genes involved in nucleic acid metabolism, including genes *Bhs3_009* (79), *Bhs211_042* (50), *Bhs3_092* (43) and *Bhs6835_002* (42) (Table 1). Obviously, by adopting the data-driven strategy, the Bayesian network not only verified the previous three gene clusters, but also discovered the key controlling genes in *B. hygrometrica* regarding to the dehydration response.

Besides, we also found out seven genes directly response to stress, including genes *Bhs85_075* (71), *Bhs2169_013* (61), *Bhs62_045* (54), *Bhs6354_003* (52), *Bhs1230_006* (44), *Bhs109_092* (43) and *Bhs161_011* (41) (Table 1). The results demonstrate that the data-driven strategy based on the Bayesian network is efficient in discovering the important genes in the transcriptome analysis.

Table 1. Important dehydration response genes in *B. hygrometrica*.

Gene	Degree	Biological Process
Bhs126_021	84	unknown
Bhs3_009	79	GO:0016070 RNA metabolic process GO:0019684 photosynthesis, light reaction GO:0015995 chlorophyll biosynthetic process GO:0043623 cellular protein complex assembly
Bhs2862_003	72	unknown
Bhs85_075	71	GO:0006950 response to stress GO:0044267 cellular protein metabolic process
Bhs1182_005	71	unknown
Bhs3124_012	71	unknown
Bhs29_019	70	GO:0006464 protein modification process GO:0007167 enzyme linked receptor protein signaling pathway
Bhs3495_020	69	GO:0051707 response to other organism GO:0031109 microtubule polymerization or depolymerization
Bhs4184_003	68	GO:0051234 establishment of localization
Bhs211_034	67	GO:0006811 ion transport
Bhs23426_001	67	unknown
Bhs1217_008	66	unknown
Bhs13204_001	66	unknown
Bhs22_072	63	GO:0015986 ATP synthesis coupled proton transport GO:0015988 energy coupled proton transport, against electrochemical gradient
Bhs942_007	63	GO:0010467 gene expression
Bhs2169_013	61	GO:0050896 response to stimulus; GO:0032446 protein modification by small protein conjugation
Bhs22_035	60	unknown
Bhs403_002	60	unknown

3.3. The Possible Function of the Gene *Bhs126_021*

The gene *Bhs126_021* has the highest degree of 84 in the gene regulatory network suggesting that it may be the most important gene in dehydration response in *B. hygrometrica* (Table 1). Unfortunately, the function of *Bhs126_021* is unknown. We attempted to uncover its function via an association analysis. Since *Bhs126_021* regulated seven genes

in the regulatory network (Table 2), we investigated the functions of the seven genes, and found that these genes involve in two of three clusters related to dehydration response, including photosynthesis and RNA metabolic process. The result suggested that *Bhs126_021* truly involved in dehydration response.

Table 2. Genes regulated *Bhs126_021*.

Gene	Degree	Biological Process
Bhs10_105	54	GO:0007127 meiosis I GO:0048229 gametophyte development
Bhs1834_026	39	unknow
Bhs250010_001	39	unknow
Bhs29_019	70	GO:0006464 protein modification process GO:0007167 enzyme linked receptor protein signaling pathway GO:0016070 RNA metabolic process
Bhs3_009	79	GO:0019684 photosynthesis, light reaction GO:0015995 chlorophyll biosynthetic process; GO:0043623 cellular protein complex assembly
Bhs3124_012	71	unknow
Bhs96_022	50	unknow

We also investigated the 38 genes with known gene function annotations regulated by the gene *Bhs126_021* in the gene regulatory network (Table 3). Among the 38 genes, 11 genes respond to stress, radiation, hormone stimulus, abiotic stimulus or osmotic stress, including genes *Bhs6354_003*, *Bhs63_076*, *Bhs3141_003*, *Bhs176_045*, *Bhs518_033*,

Bhs6596_001, *Bhs194_026*, *Bhs2167_014*, *Bhs68_058*, *Bhs1834_013* and *Bhs83_038* (Table 3). We also find genes which involve in photosynthesis (*Bhs3271_001*), DNA metabolism (*Bhs63_076*) and ABA mediated signaling pathway (*Bhs6354_003*). The results also corroborated that the gene *Bhs126_021* is a dehydration response gene.

Table 3. Genes regulated by *Bhs126_021*.

Genes	Degree	GO annotation
Bhs32_040	55	GO:0006810 transport GO:0044267 cellular protein metabolic process
Bhs942_007	63	GO:0010467 gene expression
Bhs576_011	52	GO:0010467 gene expression
Bhs3271_001	19	GO:0009639 response to red or far red light; GO:0006355 regulation of transcription, DNA-dependent GO:0018342 protein prenylation
Bhs6354_003	52	GO:2000026 regulation of multicellular organismal development GO:0009738 abscisic acid mediated signaling pathway GO:0006950 response to stress GO:0006281 DNA repair
Bhs63_076	28	GO:0009314 response to radiation GO:0048229 gametophyte development
Bhs161_031	44	GO:0006464 protein modification process
Bhs2041_014	13	GO:0008152 metabolic process GO:0009314 response to radiation
Bhs3141_003	13	GO:0006950 response to stress GO:0006631 fatty acid metabolic process
Bhs1799_014	12	GO:0006464 protein modification process GO:0023052 signaling
Bhs225_074	29	GO:0044237 cellular metabolic process GO:0050794 regulation of cellular process GO:0007275 multicellular organismal development
Bhs4430_017	12	GO:0003006 developmental process involved in reproduction GO:0009657 plastid organization GO:0009060 aerobic respiration
Bhs1655_046	12	GO:0019752 carboxylic acid metabolic process GO:0009657 plastid organization
Bhs1231_005	11	GO:0009630 gravitropism GO:0006351 transcription, DNA-dependent
Bhs176_045	11	GO:0006950 response to stress
Bhs518_033	12	GO:0009725 response to hormone stimulus

Genes	Degree	GO annotation
Bhs49_008	10	GO:0019941 modification-dependent protein catabolic process
Bhs723_010	11	GO:0010102 lateral root morphogenesis
		GO:0006605 protein targeting
Bhs18434_001	11	GO:0044248 cellular catabolic process
		GO:0007033 vacuole organization
		GO:0009856 pollination
Bhs6596_001	12	GO:0006950 response to stress
		GO:0009628 response to abiotic stimulus
		GO:0045229 external encapsulating structure organization
		GO:0048588 developmental cell growth
Bhs194_026	12	GO:0009250 glucan biosynthetic process
		GO:0042546 cell wall biogenesis
		GO:0006950 response to stress
Bhs547_042	11	GO:0008152 metabolic process
Bhs3268_008	10	GO:0051234 establishment of localization
Bhs63_048	10	GO:0008152 metabolic process
Bhs2169_007	10	GO:0009987 cellular process
Bhs238_018	8	GO:0006351 transcription, DNA-dependent
Bhs6215_001	10	GO:0009755 hormone-mediated signaling pathway
		GO:0009908 flower development
Bhs109_094	12	GO:0048513 organ development
		GO:0050794 regulation of cellular process
		GO:0006351 transcription, DNA-dependent
Bhs2167_014	8	GO:0006950 response to stress
		GO:0051604 protein maturation
Bhs68_033	7	GO:0045229 external encapsulating structure organization
		GO:0044238 primary metabolic process
Bhs68_058	10	GO:0006950 response to stress
		GO:0003006 developmental process involved in reproduction
Bhs161_050	8	GO:0006464 protein modification process
Bhs353_008	9	GO:0044238 primary metabolic process
Bhs8864_001	8	GO:0006073 cellular glucan metabolic process
Bhs334_013	9	GO:0009250 glucan biosynthetic process
Bhs1834_013	11	GO:0032501 multicellular organismal process
		GO:0006970 response to osmotic stress
Bhs83_038	8	GO:0006970 response to osmotic stress

4. Conclusions

The data-driven strategy based on the Bayesian network approach could not only find out the knowledge obtained by the knowledge-driven strategy, but also could discover the novel knowledge in transcriptome data.

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