Abstract. The aim of the present study was to construct a mathematical model to predict the changing trends of cardiac hypertrophy at gene level. Microarray data were downloaded from Gene Expression Omnibus database (accession, GSE21600), which included 35 samples harvested from the heart of Wistar rats on postoperative days 1 (D1 group), 6 (D6 group) and 42 (D42 group) following aorta ligation and sham operated Wistar rats, respectively. Each group contained six samples, with the exception of the samples harvested from the aorta ligated group after 6 days, where n=5. Differentially expressed genes (DEGs) were identified using a Limma package in R. Hierarchical clustering analysis was performed on common DEGs in order to construct a linear equation between the D1 and D42 groups, using linear discriminant analysis. Subsequent verification was performed using receiver operating characteristic (ROC) curve and the measurement data at day 42. A total of 319, 44 and 57 DEGs were detected in D1, D6 and D42 sample groups, respectively. AKIP1,ANKRD23,LTBP2,TGF-β2 and TNFRSF12A were identified as common DEGs in all groups. The predicted linear equation between D1 and D42 group was calculated to be y=1.526x -186.671. Assessment of the ROC curve demonstrated that the area under the curve was 0.831, with a specificity and sensitivity of 0.8. As compared with the predictive and measurement data at day 42, the consistency of the two sets of data was 76.5%. In conclusion, the present model may contribute to the early prediction of changing trends in cardiac hypertrophy disease at gene level.

Introduction

Cardiac hypertrophy is associated with the thickening of the heart muscle (1) and the risk factors of cardiac hypertrophy include hypertension, obesity, muscular dystrophy, cardiomyopathy or heart failure (2). Furthermore, it has been demonstrated that genetic factors and signaling pathways may participate in the pathogenesis of cardiac hypertrophy, which may be associated with an enhanced risk of sudden cardiac death and cardiovascular mortality (3,4). As the early symptoms of this disease are difficult to detect, it is crucial that novel molecular markers for the early therapy of cardiac hypertrophy are identified.

Molecular markers of cardiac hypertrophy have been identified (5). In particular, Kontaraki et al (6) identified GATA4, myocardin and β-mysosin heavy chain as early cardiac marker genes. Furthermore, smooth muscle α-actin has been demonstrated to be a molecular marker for pressure-overload hypertrophy (7). Using mouse models, Qing et al (8) have previously reported that miR-22 serves a crucial function in the regulation of cardiac hypertrophy and cardiac remodeling. Fibroblast growth factor 21, which is an endocrine factor, has a protective role in cardiac cells (9). As an increasing number of molecular markers are identified, mathematical models can be constructed to predict the risk of cancer (10).

Various types of mathematical models have contributed to the prediction of diseases. Flux balance models of cellular metabolism have been used to analyze and predict transcriptional regulation under certain conditions, including catabolite repression and amino acid biosynthesis pathway repression (11). Furthermore, various genes and pathways associated with differentiation, including MAOA and ADH1B metabolic genes in human pulmonary type II cells (12) and nuclear factor-kappaB pathway in a mouse model of genitourinary inflammation (13), have been identified via mathematical cluster analysis using GENECLUSTER, which is a publicly available computer package that contributed to the establishment of an effective treatment for acute promyelocytic leukemia (14). According to a previous study conducted by Kondo and Miura (15), the reaction-diffusion model is effective in biological pattern formation. Thus, these previous studies suggest the mathematical modeling is a useful tool for the prediction of disease.

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Key words: cardiac hypertrophy, hierarchical clustering analysis, linear discriminant analysis, mathematical model, receiver operating characteristic curve
Using microarray data downloaded from the Gene Expression Omnibus (GEO) database (accession, GSE21600), which included 35 heart samples harvested from a Wistar rat on postoperative days 1, 6 and 42 following aorta ligation and sham-operated Wistar rats, respectively. Hellman et al (16) demonstrated a correlation between hyaluronan concentration and specific gene expression levels using SPSS software. Analysis of the correlation matrix was performed according to the Principal components method (17), and orthogonal partial least squares-discrimination analysis was used to analyze the datasets of GSE21600, in which the previous clustering, including extracellular matrix and adhesion molecules were confirmed, and fatty acid metabolism, glucose metabolism, mitochondria and atherosclerosis were detected as the new clustering (18). However, these previous two studies failed to predict the changing trends of genes in this disease. Hence, the present study aimed to reanalyze the expression profiles of GSE21600 in order to construct a predictive model of cardiac hypertrophy using linear discriminant analysis (LDA) method. GSE21600 microarray data was used to identify differentially expressed genes (DEGs) using a Llima package in R (version. 3.26.5), which calculates linear models of microarray data. Common DEGs were used to construct a mathematical model in order to predict the expression levels of genes in the cardiac hypertrophy samples. The mathematical model was verified receiver operating characteristic (ROC) curve and the consistency of predictive and measurement data. The present study may be useful for the early prediction of changing trends in cardiac hypertrophy disease at the gene level.

Materials and methods

Data preprocessing and DEGs screening. GSE21600 microarray data were downloaded from the GEO database (http://www.ncbi.nlm.nih.gov/geo/) (16). GSE21600 included data from 35 heart samples harvested from 36 Wistar rats which were excised on postoperative days 1, 6 and 42 following aorta ligation and sham-operated groups, respectively. Each group contained six samples at each time point, with the exception of the samples harvested from the aorta ligated group at 6 days, where n=5. The microarray platform of GSE21600 was Illumina GPL6101 RatRef -12 expression bead chip (version 1.0; Illumina, Inc., San Diego, CA, USA).

Samples were divided into three groups: Day 1 (D1), day 6 (D6) and day 42 (D42). DEGs between the postoperative and sham-operated samples were identified in these three groups, respectively. Firstly, normalization of the microarray data was performed in the R language (19,20), and DEGs were subsequently identified using a Limma package in R (21). False discovery rate (FDR) was used to adjust the P-value, according to the method outlined by Benjamini and Hochberg (22). FDR<0.05 and >1 log₂ fold change (FC) were chosen as the cut-off criteria.

Specific gene screening. In order to screen the specific expression levels of genes at each time point, DEGs were compared between the two groups. Subsequently, hierarchical clustering analysis (23) was performed on the common DEGs in the three groups.

| Gene           | Day 1            | Day 6            | Day 42           |
|----------------|------------------|------------------|------------------|
| AKIP1          | -1.24914         | -1.36699         | -1.80092         |
| ANKRD23        | -2.90253         | -3.69624         | -2.85077         |
| LTB2P2         | -3.68846         | -4.20566         | -2.02513         |
| TGF Beta4      | -2.15313         | -2.11814         | -1.75841         |
| TNFRSF12A      | -1.99987         | -2.08827         | -1.54923         |

Sorting algorithm and construction of the mathematical model. Linear discriminant analysis (LDA) is a method that is commonly widely used in microarray classification to obtain discrimination function. LDA analysis can be performed when there are ≥2 groups and each group contains ≥2 variables (24,25). In this method, a linear equation based on the variations in the two groups is established: Y = a + b₁x₁ + b₂x₂ +...+ bₙxₙ, where 'a' represents a constant and 'b₁,b₂,... and bₙ' represents the regression coefficient. In the present study, the cardiac hypertrophy samples were defined as ‘1’ and the control samples were defined as ‘-1’. Based on the dynamic expression changes of the common DEGs detected in the D1 group, the expression pattern in the D42 group was predicted via the calculated mathematical model constructed using the LDA method (26).

Verification of the mathematical model. Disease classification models are typically determined using multivariate regression analysis (27,28), ROC curve (29-32) or prospective validation (33). ROC curve was used in the present study in order to evaluate the discriminant effect of the mathematical model and directly observe the accuracy of the present analysis method. Indices, including specificity and sensitivity, were calculated in order to estimate the predictive ability of LDA, in addition to area under the curve (AUC) of the ROC curve, which was also calculated to estimate accuracy. In the present study, AUC was used to distinguish non-accuracy (AUC≤0.5), low accuracy (0.5<AUC≤0.7), moderate accuracy (0.7<AUC≤0.9) and high accuracy (0.9<AUC<1). Furthermore, by comparing the prediction data with the measurement data in the D42 samples, the consistency of two sets of data was evaluated.

Results

Identification, comparison and feature selection of DEGs. Normalization of the microarray data is presented in Fig. 1. DEGs were identified, and the genes with FDR<0.05 and >1 log₂ FC were considered as differentially expressed between the ligated samples and sham-operated samples. A total of 319, 44 and 57 DEGs were identified in the D1, D6 and D42 groups respectively.

A total of 23 DEGs were detected between the D1 and D6 groups, 14 DEGs were detected between the D1 and D42 groups, and five DEGs were identified between the D6 and D42 groups. Five common DEGs, including A kinase interacting protein 1 (AKIP1), ankyrin repeat domain 23
Table II. Predicted data at day 42 using a linear equation of the gene expression levels of cardiac hypertrophy.

| Gene accession | State | Expression on day 1 | Expression on day 42 | Predicted on day 42 |
|----------------|-------|---------------------|----------------------|---------------------|
| GSM539275      | 1     | 332.1987            | 337.3279             | 326.1898781        |
| GSM539276      | 1     | 272.2375            | 126.1764             | 235.327208         |
| GSM539277      | 1     | 485.7471            | 792.9784             | 558.8706386        |
| GSM539278      | 1     | 778.9512            | 344.6311             | 1,003.179749       |
| GSM539279      | 1     | 320.8331            | 108.7458             | 308.9696297        |
| GSM539280      | 1     | 716.3563            | 479.7876             | 908.3268089        |
| GSM539281      | -1    | 85.13754            | 66.26252             | -48.1961965        |
| GSM539282      | -1    | 71.55708            | 13.26508             | -68.775425         |
| GSM539283      | -1    | 50.69723            | 41.25237             | -100.385561        |
| GSM539284      | -1    | 23.54682            | 75.99313             | -141.528123        |
| GSM539285      | -1    | 124.7012            | 29.73599             | 11.7569297         |
| GSM539286      | -1    | 49.61586            | 52.55618             | -102.024223        |
| GSM539275      | 1     | 4,201.869           | 6,190.12481          | 6,190.12481        |
| GSM539276      | 1     | 1,882.365           | 5,415.158            | 2,675.24642        |
| GSM539277      | 1     | 3,337.275           | 9,621.91             | 4,879.955589       |
| GSM539278      | 1     | 3,016.572           | 4,621.265            | 4,393.975807       |
| GSM539279      | 1     | 2,658.368           | 3,865.638            | 3,851.68593        |
| GSM539280      | 1     | 1,956.894           | 8,021.108            | 2,788.184519       |
| GSM539281      | -1    | 1,219.844           | 959.4762             | 1,671.290077       |
| GSM539282      | -1    | 1,070.036           | 1,546.261            | 1,444.277361       |
| GSM539283      | -1    | 1,341.854           | 1,415.456            | 1,992.561078       |
| GSM539284      | -1    | 1,024.116           | 3,023.837            | 1,374.692133       |
| GSM539285      | -1    | 988.543             | 1,751.745            | 1,320.786311       |
| GSM539286      | -1    | 1,213.691           | 2,605.091            | 1,661.966081       |
| GSM539275      | 1     | 880.5447            | 147.3087             | 1,157.130248       |
| GSM539276      | 1     | 126.5936            | 169.5375             | 14.62459301        |
| GSM539277      | 1     | 1,011.612           | 281.1071             | 1,555.744099       |
| GSM539278      | 1     | 1,073.774           | 185.5347             | 1,449.941769       |
| GSM539279      | 1     | 340.023             | 62.10585             | 338.046919         |
| GSM539280      | 1     | 122.0065            | 237.4351             | 7.673495398        |
| GSM539281      | -1    | 36.33411            | 32.24878             | -122.150826        |
| GSM539282      | -1    | 50.67635            | 24.24548             | -100.417201        |
| GSM539283      | -1    | 36.68185            | 45.16885             | -121.623876        |
| GSM539284      | -1    | 30.85578            | 71.55927             | -130.452456        |
| GSM539285      | -1    | 15.40947            | 32.20256             | -153.859142        |
| GSM539286      | -1    | 34.06184            | 51.90232             | -125.594128        |
| GSM539275      | 1     | 1,915.488           | 1,621.039            | 2,725.439616       |
| GSM539276      | 1     | 719.9728            | 1,732.95             | 913.8063723        |
| GSM539277      | 1     | 1,491.145           | 1,375.875            | 2,082.408155       |
| GSM539278      | 1     | 2,425.283           | 3,341.205            | 3,497.961428       |
| GSM539279      | 1     | 1,208.035           | 885.0079             | 1,653.395218       |
| GSM539280      | 1     | 1,999.254           | 1,564.762            | 2,852.375074       |
| GSM539281      | -1    | 391.4185            | 495.3794             | 415.929062         |
| GSM539282      | -1    | 355.6202            | 400.3427             | 361.681301         |
| GSM539283      | -1    | 437.2545            | 578.2272             | 485.3870006        |
| GSM539284      | -1    | 215.4012            | 719.1659             | 149.2135176        |
| GSM539285      | -1    | 464.529             | 402.5466             | 526.717626         |
| GSM539286      | -1    | 483.1193            | 857.3302             | 554.8885815        |
| GSM539275      | 1     | 1,776.678           | 768.9708             | 2,515.092804       |
| GSM539276      | 1     | 998.7648            | 732.2133             | 1,336.275995       |
| GSM539277      | 1     | 2,373.809           | 1,362.486            | 3,419.959903       |
| GSM539278      | 1     | 3,322.548           | 1,513.086            | 4,857.638915       |
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(ANKRD23), latent transforming growth factor beta binding protein (LTBP2), transforming growth factor (TGF)-β2 and tumor necrosis factor receptor superfamily member 12a (TNFRSF12A), were identified among the three groups (Fig. 2).

Clustering analysis of the five common DEGs demonstrated that the sham operated and ligated samples were respectively clustered together; however, three ligated samples (16.67%; 3/18) were mixed into the operated group and two sham-operated samples (11.76%; 2/17) were mixed into the ligated group (Fig. 3). These five common DEGs were identified as downregulated genes (Table I).

**Construction and verification of the mathematical model.** Based on the expression levels and dynamic changes detected in the five common DEGs, a linear equation between the D1 and D42 groups was calculated as follows: 

\[ y = 1.526x - 186.671 \]

where \( y \) and \( x \) represent the expression levels in the D42 and D1 groups, respectively.

Assessment of the ROC curve demonstrated that AUC was 0.831, which indicated that the predictive accuracy was 83.1% and the specificity and sensitivity were 0.8, respectively (Fig. 4A). By comparing the predictive and measurement data

| Gene accession | State | Expression on day 1 | Expression on day 42 | Predicted on day 42 |
|----------------|-------|---------------------|----------------------|---------------------|
| GSM539279      | 1     | 879.2261            | 513.2602             | 1,155.132097        |
| GSM539280      | 1     | 1,201.621           | 1,250.521            | 1,643.675713        |
| GSM539281      | -1    | 411.144             | 251.4373             | 445.8202516         |
| GSM539282      | -1    | 375.7809            | 208.7139             | 392.2325034         |
| GSM539283      | -1    | 406.536             | 168.1061             | 438.837483          |
| GSM539284      | -1    | 297.8341            | 399.4494             | 274.1152146         |
| GSM539285      | -1    | 322.7278            | 352.2844             | 311.8380763         |
| GSM539286      | -1    | 316.283             | 400.1669             | 302.0718985         |

1, the aorta ligated operation group; -1, the sham operated group.
at 42 days (Table II), the consistency of these two datasets was calculated to be 76.5% (Fig. 4B).

Discussion

In the present study, the expression profiles of sham operated and ligated heart samples harvested from a Wistar rat were analyzed and 319, 44 and 57 DEGs were subsequently identified in the D1, D6 and D42 groups, respectively. **AKIP1, ANKRD23, LTBP2, TGF-β2 and TNFRSF12A** were identified as common DEGs among the three groups, and their association with cardiac hypertrophy has previously been demonstrated (34-37). **AKIP1** was identified as a key regulator of heart function via the cAMP-dependent protein kinase signaling pathway (38). During periods of the oxidant stress, the expression of **AKIP1** is capable of protecting cardiac myocytes from the ischemic injury via enhanced mitochondrial integrity (38). Furthermore, the expression of **AKIP1** may also protect the heart via mitochondrial stress adaptation (39), and it has been demonstrated that mitochondrial DNA damage may contribute to the development of cardiac hypertrophy and heart failure (40). These results suggested that **AKIP1** may serve a crucial function in the development of cardiac hypertrophy via mitochondrial stress adaptation mechanisms. Hellman et al (16) have previously demonstrated that **LTBP2** and **TGF-β2** are associated with the development of cardiac hypertrophy. **LTBP2**, which belongs to the fibrillin superfamily, regulates the release of **TGF-β1** (41,42). Previous studies have demonstrated that **TGF-β**, including **TGF-β1, TGF-β2** and **TGF-β3**, have an important role in the pathogenesis of cardiac hypertrophy by stimulating the proliferation of cardiomyocytes (43,44). These
results demonstrated that LTBP2 and TGF-β2 are associated with the regulation of cardiac hypertrophy. However, the role of ANKR2D3 and TNFRSF12A in the development of cardiac hypertrophy is yet to be elucidated. As the results of the present study demonstrated that they were detected as common genes in the three groups, we hypothesize that AKIPI1, ANKR2D3, LTBP2, TGF-β2 and TNFRSF12A may contribute to the development of cardiac hypertrophy.

Numerous mathematical techniques have been developed in order to analyze large datasets, and mathematical modeling is a useful and powerful tool for the analysis of gene expression patterns (14). LDA is a well-known multivariate technique that is used for dimension reduction and classification (45). A 3-gene model, TNFRSF8, BATF3 and TMOD1, which was obtained by LDA and leave-one-out cross-validation, was previously used to separate ALK (-) and anaplastic large-cell lymphoma from peripheral T-cell lymphoma, and the accuracy of the model was ~97% (46). Furthermore, a class-prediction model of patients with Graft-vs-host disease was previously constructed using LDA, and the accuracy was 63-80%, as estimated by reverse transcription-quantitative polymerase chain reaction (47). ROC, which directly displays the correlation of specificity and sensitivity can be used to assess the accuracy of diagnostic tests (48). In a previous study conducted by Barretina et al (49), Cancer Cell Line Encyclopedia, which is a predictive model, was cross-validated by specificity and sensitivity of the ROC curve and used to predict the drug response to gene expression, including topoisomerase inhibitors associated with Schlafen family member 11. Similarly, a predictions model has previously been constructed for dementia using in-depth editing and language assistance.

In the present study, 319, 44 and 57 DEGs were detected in D1, D6 and D42 groups, respectively. AKIPI1, ANKR2D3, LTBP2, TGF-β2 and TNFRSF12A were identified as common DEGs. A linear equation was calculated between the D1 and D42 groups, as follows: y=1.526x-186.671. This linear equation, which acted as a prediction model of gene expression levels, may contribute to the early prediction of the changing trends in cardiac hypertrophy disease.

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