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Comparing classification performance of several types of significant genes to identify key genes in uremia

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Abstract. – OBJECTIVE: End-stage renal failure has profound changes in human gene expressions, but the molecular causation of these pleomorphic effects termed uremia is poorly understood. The purpose of this study was to explore key genes in uremia by comparing classification performance of five kinds of significant genes based on the support vector machines (SVM) model.

MATERIALS AND METHODS: The five kinds of genes were differentially expressed genes (DEGs), differential pathway genes (DPGs), common differential genes between DEGs and DPGs (CDGs), hub genes (HUGs) and common genes of hub genes and DEGs (CHDGs). In detailed, DEGs were detected by linear models for microarray data (Limma) package. Attract method was utilized to capture DPGs from differential pathways. HUGs were determined according to topological centrality analysis of mutual information network (MIN). Subsequently, SVM model was implemented to assess the classification performance of DEGs, DPGs, CDGs, HUGs and CHDGs, depending on its induces the area under the receiver operating characteristics curve (AUC), true negative rate (TNR), true positive rate (TPR) and the Matthews coefficient correlation classification (MCC).

RESULTS: A total of 166 DEGs, 597 DPGs, 13 CDGs, 29 HUGs and 10 CHDGs were obtained in uremia. By assessing the SVM model classification analysis, CHDGs had the best performance of all with AUC = 0.99, TNR = 1.00, TPR = 0.97 and MCC = 0.95. Hence, we considered the CHDGs as key genes in uremia.

CONCLUSIONS: Key genes concluded in this investigation might provide vital insights into uremia progression and new therapies.

Key Words: Uremia, Genes, Attract, Hub, Mutual information network, Support vector machines.

Introduction

Uremia is a disorder that accompanies kidney failure, chronic kidney disease, systemic inflammation and immune deficiency[1,2]. Its illness is considered to be due largely to the accumulation of organic waste products along with the complications of treatment and continued inorganic ion disturbances that are normally cleared by the kidneys[3,4]. A substantial number of publications have attributed to the investigations of the concentration changes of individual uremic retention solutes. However, the molecular changes underlying uremia remain unclear.

Developments of high-throughput technology have allowed us to acquire gene expression data, reveal guiding principles of the molecular initiation and progression and these provide help for exploring potential molecular biomarkers of biological dysfunction for early detection and therapy of uremia[5,6]. For instance, Tanaka et al had reported that Glu/Asp-rich carboxy-terminal domain 2 (*CITED2*) played an important role in the progression of uremia[7]. But the amount of biomarkers is still very small and, thus, these markers could not meet to the great need of target treatment for uremia.

Therefore, in the current investigation, we aimed to investigate key genes which might be potential biomarkers in uremia by comparing classification performance of different kinds of significant genes based on the support vector machines (SVM) model. To achieve this goal, we identified five types of significant genes for uremia based on gene expression data, differentially expressed genes (DEGs), differential pathway genes (DPGs), common differential genes between DEGs and DPGs (CDGs), hub genes (HUGs) and common genes of hub genes and DEGs (CHDGs). Subsequently, classification performances for them were evaluated using SVM induces which included the area under the receiver operating characteristics curve (AUC), the Matthews coefficient correlation classification (MCC), true negative rate (TNR) and true positive rate (TPR). Finally,

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we selected one kind of significant genes with the best performance as key genes which would be applicable to its early detection and treatment for uremia.

Materials and Methods

Gene Expression Data

In this study, uremic-related gene expression profile with accessing number E-GEOD-37171 was downloaded from ArrayExpress database. E-GEOD-37171, which presented on A-AFFY-44 – Affymetrix GeneChip Human Genome U133 Plus 2.0 [HG-U133_Plus_2] Platform, was comprised of 75 uremia samples and 40 normal samples. Before the analysis, we removed invalid and duplicated probes by feature filter method in genefilter package[8], and then converted data on probe levels into gene symbols through annotate package[9]. A total of 20542 genes were obtained in the gene expression data for further exploitation.

DEGs

In order to identify DEGs between uremia and normal controls, linear models for microarray data (Limma) package was applied[10]. Here, Limma is a Bioconductor software package that provides an integrated solution for analyzing data from gene expression experiments. Only genes who met to the thresholds of p-value ≤ 0.01 and $|\log_2\text{FoldChange}| \geq 2$ were defined as DEGs of uremia.

DPGs and CDGs

To examine differential pathways between normal and uremia conditions, an attractor approach developed by Mar et al[11] was utilized. The method composed four parts[12]: determining core Kyoto encyclopedia of genes and genomes (KEGG) pathways that discriminated the most strongly between cell types or experimental groups of interest; finding different synexpression groups that were present within a core attractor pathway; identifying sets of genes that showed highly similar profiles to the synexpression groups within an attractor pathway module; and testing for functional enrichment for each of the synexpression groups to detect any potentially shared pathways.

In detailed, the KEGG pathways for gene expression profile were obtained based on the Database for Annotation, Visualization and Integrated Discovery (DAVID)[13] and pathways with less than 5 genes were removed. The core pathways were identified through the F-statistic, for gene i, $F^{(i)}$ was computed:

$$F^{(i)} = \frac{\frac{1}{K-1}\sum_{k=1}^{K} r_k \left[y_{\bullet k}^{(i)} - y_{\bullet\bullet}^{(i)} \right]^2}{\frac{1}{N-K}\sum_{k=1}^{K}\sum_{j=1}^{rj} \left[y_{jk}^{(i)} - y_{\bullet\bullet}^{(i)} \right]^2}$$

where j represented corresponding expression value in each replicate sample; r_k for each cell type $k = 1, \ldots, K$; y stood for the mixed effect model; N meant the total number of samples. Large values of the F-statistic indicated a strong association whereas a small F-statistic suggests that the gene demonstrated minimal cell type-specific expression changes. To make the F-statistic more confidence, we selected t-test to correct the $\log_2$-transformed F-statistics and obtain a p-value for each potentially shared pathway which originated from synexpression groups. Adjusting their p-values on the basis of false discovery rate (FDR)[14], we defined the top 5 pathways (in descending order of p-values) were differential pathways and the genes enriched in differential pathways were denoted as DPGs. In addition, common genes between DEGs and DPGs were denoted as CDGs.

HUGs and CHDGs

Based on DPGs, a mutual information network (MIN) was constructed to identify HUGs, which typically relied on the estimation of mutual information (MI) between all pairs of variables[15]. First of all, we computed a mutual information matrix (MIM), a square matrix whose i, j-th element was the MI between the random genes X_i and X_j. Secondly, the computation of an edge score for each pair of nodes was conducted by the context likelihood of relatedness (CLR) algorithm which was an extension of the relevance network approach[15] and computed the MI for each pair of genes and derived a score related to the empirical distribution of the MI values[16]. In particular, instead of considering the information $I(X_i; X_j)$ between genes X_i and X_j, it took into account the edge score z_{ij}:

$$z_{ij} = \sqrt{z_i^2 + z_j^2}$$

of which

$$z_i = \max\left(0, \frac{I(X_i; X_j - \mu_i)}{\sigma_i}\right)$$

where μ_i and σ_i represented respectively the sample mean and standard deviation of the empirical distribution of the values $I(X_i; X_j)$. Finally, inputting the genes and edge scores into the igraph software package[17], to visualize the MIN.

For the purpose of detecting significant genes in the MIN, topological centrality index (degree) was implemented in our paper. Degree quantifies the local topology of each gene by summing up the number of its adjacent genes and gives a simple count of the number of interactions of a given node[18]. HUGs of MIN were defined as genes with degree ≥ 455. Besides, common genes between HUGs and DEGs were denoted as CHDGs.

Classification and Evaluation

After obtaining five kinds of significant genes (DEGs, DPGs, CDGs, HUGs and CHDGs) for uremia by different methods, a SVM classifier was developed to evaluate the classification performance of them for 75 uremia samples and 40 normal samples. We divided these samples into two groups (train set and test set) by keeping to the percentage of 3:2 randomly. A 5-fold cross-validation was conducted on the train set to evaluate the potential classification strength of the models, and then we computed its prediction on the separate test set. Four induces of SVM evaluation was utilized, AUC, MCC, TNR and TPR.

In detailed, accuracy (ACC) is one of the most popular performance measures in machine learning classification, but it does not take into account the nature of the incorrect predictions[19]. Thus, we engaged the AUC which had been introduced as a better measure for evaluating the predictive ability of machine learners than ACC[20]. MCC was a measure of the quality of binary classification and considered the true and false positive and negatives[21]. Additionally, TNR or specificity represented the ratio of correctly classified negatives to the actual number of negatives, as well as TPR or sensitivity, which was defined to be the ratio of positives correctly classified to the actual number of positives[22].

$$\mathrm{TNR} = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FP}} \times 100\%$$

$$\mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}} \times 100\%$$

of which TP (true positive) represented the number of positive samples correctly predicted as positive; TN (true negative) stood for the number of negative samples correctly predicted as negative; FP (false positive) was the number of negative samples incorrectly predicted as positive; and FN (false negative) on behalf of the number of positive samples incorrectly predicted as negative. The combination of those measures gave us an adequate overview of the classification's performance. One of the five types with the best performance was regarded as the key genes of uremia.

Results

DEGs

Using the pre-processed gene expression data which was consisted of 20542 genes, a total of 166 DEGs between uremia and normal controls were identified using Limma package with the thresholds of p-value ≤ 0.01 and $|\log_2\mathrm{FoldChange}| \geq 2$. The top 100 DEGs were listed in Table I, the most significant five DEGs were *YWHAE* (p = 8.65E-29), *HINT1* (p = 8.75E-29), *RBBP4* (p = 2.34E-28), *PKN2* (p = 2.21E-26) and *SLC25A32* (p = 5.29E-25).

DPGs and CDGs

There were 1431 human biological pathways in KEGG pathway database, after removing the invalid and duplicated pathways, and only 300 pathways enriched by 6919 genes remained. When mapping 20542 genes to the 300 pathways, we obtained pathways enriched by genes in the gene expression profile. Due to pathways with a too small number of genes were not easily understood. Thus, we filtrated the pathways with the number of enriched genes < 5, and a total of 277 pathways were retained to identify differential pathways by utilizing attractor method. Ranking these pathways in descending order of p-value, the top 5 pathways were mRNA surveillance pathway, Spliceosome path-

Table I. Top 100 differentially expressed genes (DEGs) for uremia.

No.	Gene	No.	Gene	No.	Gene	No.	Gene
1	YWHAE	26	NUP160	51	ZEB2	76	WDFY1
2	HINT1	27	RRN3	52	THAP9-AS1	77	NDFIP1
3	RBBP4	28	UBP1	53	HEATR5A	78	GIMAP6
4	PKN2	29	EIF2AK3	54	TCERG1	79	SLBP
5	SLC25A32	30	SUCLG2	55	CMTR2	80	TMEM106B
6	CHORDC1	31	WDR11	56	TMEM168	81	ANKRD10
7	LRIF1	32	ADSS	57	EBLN3	82	FKBP1B
8	RPS11	33	SRSF10	58	FUBP3	83	SOAT1
9	EPB41L3	34	TBL1XR1	59	SGPP1	84	ASUN
10	C12orf66	35	RPS24	60	STAM	85	UFL1
11	ACTL6A	36	CSNK1A1	61	ALG13	86	SEC24B
12	SLC25A37	37	XPOT	62	AASDHPPT	87	EIF3A
13	ZFP36L2	38	FOS	63	PXYLP1	88	MDM1
14	ATF1	39	INPP4A	64	PRNP	89	HNRNPA3
15	SLMO2	40	BORCS7	65	GMCL1	90	TOB1
16	THEMIS	41	SRPK2	66	SCAF8	91	ITGA4
17	TOX	42	ISOC1	67	YWHAZ	92	UBA2
18	LACTB	43	PSMA3-AS1	68	CLEC2D	93	GSAP
19	YTHDF3	44	ATE1	69	SP1	94	TCF12
20	CCDC117	45	HSF2	70	SHPRH	95	SUCLA2
21	EXOC5	46	RNF38	71	C16orf72	96	CCNT2
22	TPD52	47	MAP3K8	72	ZNF518A	97	UBE2Q2
23	VPS37A	48	MED4	73	C4orf32	98	FAM3C
24	TMF1	49	RASSF5	74	LINC01215	99	SMNDC1
25	UPF3A	50	FBXO3	75	CRY1	100	MYBL1

way, RNA transport pathway, Epstein-Barr virus infection pathway and Ribosome pathway, and were recognized as differential pathways between uremia and normal controls. Further, 597 genes enriched in the 5 differential pathways were denoted as DPGs.

By taking intersections between DEGs and DPGs, 13 CDGs were obtained in total, which comprised *UPF3A*, *XPOT*, *TCERG1*, *RPS11*, *RPS24*, *SMNDC1*, *NUP160*, *YWHAZ*, *YWHAE*, *EIF3A*, *HNRNPA3*, *SRSF10* and *EIF2AK3*.

HUGs and CHDGs

To further explore functions and significance of DPGs, a MIN was constructed through CLR algorithm based on them (Figure 1). There were 591 nodes and 4496 edges. After carrying out topological centrality analysis for the MIN, the HUGs with degree ≥ 455 were displayed in Table II. *XPOT* (Degree = 484), *TCERG1* (Degree = 481), *HNRNPA3* (Degree = 474), *EIF2AK3* (Degree = 473) and *PPP2CA* (Degree = 473) were the top five ranked genes dependent on degree distribution.

By extracting the common genes between HUGs and DEGs, we gained 10 CHDGs, and they were *RPS24*, *SMNDC1*, *EIF3A*, *YWHAZ*, *TCERG1*, *SRSF10*, *HNRNPA3*, *XPOT*, *NUP160* and *EIF2AK3*.

Classification and Evaluation

In this paper, we obtained five kinds of significant genes (DEGs, DPGs, CDGs, HUGs and CHDGs) for uremia by different methods, to compare the performance of them on uremia and normal controls, SVM analysis was utilized, and the results were showed in Table III. We found that CHDGs had the best classification performance between uremia samples and normal controls with

Table II. Hub genes (HUGs) associated with uremia.

Gene	Degree	Gene	Degree
XPOT	484	CPSF6	462
TCERG1	481	RPS24	462
HNRNPA3	474	YWHAZ	462
EIF2AK3	473	PSMD12	461
PPP2CA	472	CLNS1A	460
NUP133	470	HNRNPK	459
NUP160	467	EIF2B1	459
SNRPA1	465	SRSF10	458
IKBKB	465	EIF3A	458
SMNDC1	465	RAN	457
TRA2B	465	CDKN1B	457
YWHAQ	465	PRPF4	456
RBM22	464	YWHAG	455
CRNKL1	463	DHX15	455
U2SURP	484		

AUC = 0.99, TNR = 0.95, TPR = 1.00 and MCC = 0.97. Therefore, the CHDGs were considered to be key genes in the progress of uremia.

Discussions

Traditionally, potential diagnostic or prognostic markers is usually obtained by identification of the most significant DEGs in the high-throughput case-control studies[23]. But it has been demonstrated that the most significant DEGs obtained from different studies for a particular disease are typically inconsistent resulting from multiple problems, due to small sample size, measurement error, and different statistical methods[24,25]. And the overlap is very low for the most significantly dysregulated genes across multiple studies[26]. To overcome this problem, one could evaluate DEGs for disease-association using a network strategy[27], or mapped them to a certain molecular pathway, for the reason that DEGs in complex cancer were not worked alone, network and pathway approach could offer effective means to connect them together. Therefore, in the present study, we compared DEGs with other genes to investigate key genes in uremia.

A total of five kinds of significant genes for uremia were identified, which included DEGs detected by Limma package, DPGs identified

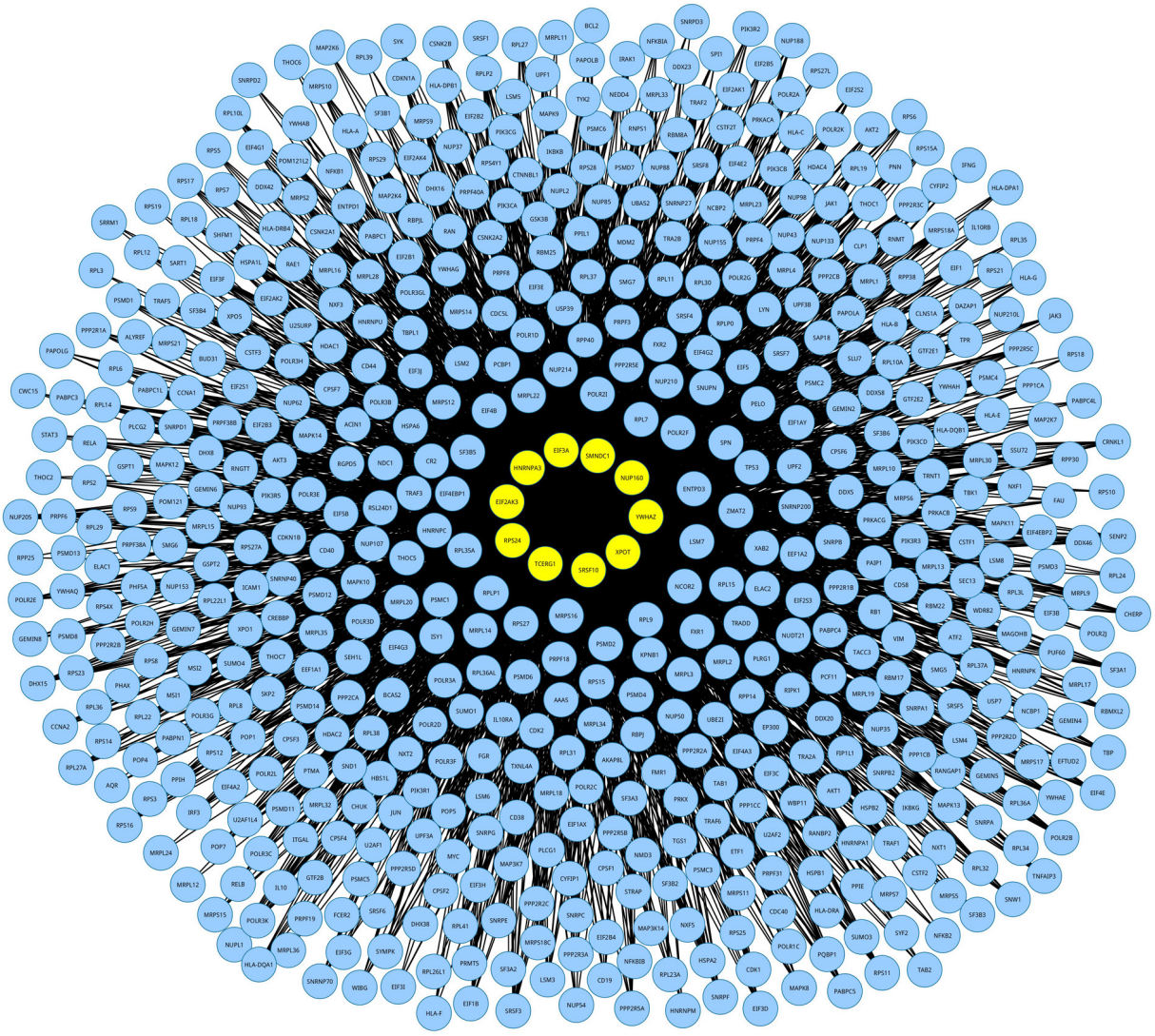

Figure 1. Mutual information network (MIN) for differential pathway genes (DPGs) based on the context likelihood of relatedness (CLR) algorithm. Nodes were genes, and edges were the interactions among two genes. The yellow nodes were common genes between hub genes (HUGs) and differentially expressed genes (DEGs), termed with CHDGs.

Table III. Classified performance of genes based on support vector machines (SVM).

	SVM model			
Genes	**AUC**	**TNR**	**TPR**	**MCC**
DEGs	0.94	0.89	0.92	0.97
DPGs	0.97	0.90	1.00	0.94
CDGs	0.96	0.85	1.00	0.91
HUGs	0.94	0.89	0.92	0.97
CHDGs	0.99	0.95	1.00	0.97

by attracting method for differential pathways, CDGs, HUGs determined according to topological centrality analysis of MIN and CHDGs. SVM model was utilized to evaluate the classification performance of them between uremia and normal samples. The results showed that 166 DEGs, 597 DPGs, 13 CDGs, 29 HUGs and 10 CHDGs were obtained in uremia. CHDGs had the best classification performance with AUC = 0.99, TNR = 0.95, TPR = 1.00 and MCC = 0.97, and thus were denoted as key genes for uremia, which covered, *SMNDC1*, *EIF3A*, *YWHAZ*, *TCERG1*, *SRSF10*, *HNRNPA3*, *XPOT*, *NUP160* and *EIF2AK3*.

These genes were mostly about gene expression and cell proliferation and differentiation, and may work at a network level. The function of these genes was illustrated as follows: *NUP160* is a vertebrate nucleoporin, which plays an important role in mRNA export[28]. *EIF3A*, an eukaryotic initiation factor, has been found both have a role in regulating translation of a subset of mRNAs and in regulating cell cycle[29]. And a recent study[30] revealed *EIF3A* may be a regulator in tumor pathogenesis and therapy response. *TCERG1*, a transcription elongation regulator, has an important role in transcriptional elongation and alternative splicing of pre-mRNAs, there has been a report demonstrated that the function of *TCERG1* can be modified by small ubiquitin-like modifier[31]. *SRSF10* is a splicing factor which functions as a sequence-specific splicing activator[32]. Over expression of *YWHAZ* has been reported to contribute the occurrence of many tumors[33-35]. And *EIF2AK3* plays a vital role in regulating insulin secretion and Ca^{2+} dynamics in β-cells[36].

To our best knowledge, not one of these genes has been previously reported to associate with uremia. However, in a recent investigation which detected the alteration of human blood cell transcriptome in uremia, they demonstrated that genes encoding regulators of transcription, mRNA transport, protein synthesis, export and cell cycle progression were significantly changed[37]. Significantly, our results were consistent with their conclusion. Furthermore, uremia patients present a marked activation of oxidative and inflammatory processes[38]. A previous report by Zhang[39] concluded that the integration of oxidative stress, inflammatory response and endoplasmic reticulum (ER) stress is critical to the pathogenesis of a variety of diseases. Either oxidative stress, or inflammatory response, or ER stress may be prominent but ultimately integrated together[39]. Among our isolated genes, *EIF2AK3* has been confirmed to be an ER stress-sensor protein[40]. Besides, physiological disorder or stimuli may disrupt protein folding reactions, producing many unfolded or misfolded proteins in the ER lumen, which was regarded as ER stress[41-46]. To deal with this disorder, cells activated a set of signal transduction pathways to alter transcriptional and translational processes[39]. Interestingly, among the key genes screened out in this investigation, several were regulated transcriptional and translational programs such as *SRSF10*, *TCERG1* and *EIF3A*. Thus, uremia may progress by the disorder of ER stress, and the oxidative stress and inflammatory response.

Conclusions

We have successfully identified 10 key genes (such as *SMNDC1*, *EIF3A* and *YWHAZ*) for uremia by comparing classification performances of five kinds of significant genes. However, how these genes coordinately regulated the processes in uremia remains unclear, and further specific investigations are still indispensable.

Conflicts of interest

The authors declare no conflicts of interest.

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