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Short Communication

Study of Genetical Genomics; a Preliminary Study

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ABSTRACT

Calculating gene clusters by various clustering approaches is usual way to study gene expression data. In recent, in vitro experiments are being conducted to use widespread applications of genetical genomics approaches in non-model and model species. Nowadays, many bioinformatics tools are under trails to make the correlation based networks to explore the genetic pathways.2000differentially expressed genes of cultured and uncultured bone cells from rabbit were taken. Network analysis was carried out from two Bioinformatics tools, BioLayout and GeneNet. David database was used to conduct functional analysis for differentially expressed genes. There were no significant overlapping functional categories between the cultured and uncultured dataset. Different genes participating in bone growth were identified. It is suggested that by using different network tools, area of genetical genomics could be explored.

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INTRODUCTION

Microarray expression data derive thousands of differentially expressed transcripts from just from very small sample size. Different factors may be involved like changes in the interests of biological system and technical artifacts to affect this sample and data obtained. General approaches which are utilized to analyze the microarray data are to derive clusters by many explorative clustering techniques or by statistically significant variations between the groups of samples to analyze the microarray data. Correlation based networks are mode to analyze the gene expression data and to see co expression in expression profiles of data. This idea have already been used by many authors and researchers (Franke*et al.*, 2006; Zhang and Horvath, 2005) by previously establishes statistical approaches like Pearson's correlation coefficient. Nowadays in-vitro studies are used to establish and study the genetical genomics in broad ranges. In genetical genomics, gene expression and marker genotype studies are done in a segregating population (Jansen, 2003; Rockman and Kruglyak, 2006). Genetic pathways are studied in gentical genomics. Genetic Pathways are made in graphical forms in which individual genes (nodes) interact and make functional linkages with other genes (graph edges). Many tools of bioinformatics are used to make these genetic pathways in form of graphical conventions. But every tool has its own limitations in giving complete biological inference because of built in computational algorithms. Nowadays different *in vivo* and *in vitro* studies are made in combinatio in wide range to see the similarity in results (Haley and Koning, 2007).

A comparison can be conducted on gene expression datasets by using network based tools GeneNet and BioLayout. In this study, cultured and uncultured osteocytes to be compared are taken from the rabbit.Aim of the study was to make the comparison between cultured and uncultured data to find out the similarities by using the data-driven, network-based approaches. So, BioLayout and GeneNet was used to make correlation based networks and after getting the results from these tools, DAVID analysis was done to make the comparison of gene annotation results of cultured versus fresh samples to find similarities and differences in the results.

MATERIALS AND METHODS

The softwares GeneNet (Schäfer*et al.*, 2006) and BioLayout (Freeman *et al.*, 2007) were used to make correlation based regulatory networks for the 2000 most significantly differentially expressed genes of cultured and uncultured bone cells of rabbit were used. GeneNet is an R package and uses the graphical Gaussian models (GGMs) while BioLayout makes the clusters by Pearson correlation coefficient. The correlation threshold 0.85 was taken to obtain the maximum number of clusters. Markov clustering algorithm (MCL) was run which is an inbuilt algorithm in this software and derive the cluster nodes by computing probability simulation. Then clusters and network was viewed by using the cluster viewer feature. Overlapping transcripts IDs among all clusters taken and subjected to the DAVID database for gene set enrichment analysis. Gene ontology tool was used to do the analysis in DAVID.

The same analysis was also conducted by using same dataset in GeneNet. Before running the GeneNet, installation of corpcor, locfdr, longitudinal and fdrtool was done (Efron, 2004). Then the generated network topology text file from GeneNet was obtained and loaded into Cytoscape (Killcoyne*et al.*, 2009) for making visualization of generated clusters and networks from GeneNet. Similarly DAVID analysis was conducted for the generated clusters in the same way as it was done in BioLayout. To get the significant annotations only P-values less than 0.05 was taken and finally a comparison was made between the significant annotations of the BioLayout and GeneNet results.

RESULTS AND DISCUSSION

When general comparison was conducted between cultured and uncultured datasets by using Microsoft Excel (2007), only 230 genes found to be overlapping among 2000 genes. DAVID analysis revealed following functional categories, negative regulation of cell

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cycle, antral ovarian follicle growth, regulation of organelle organization. Negative regulation of nuclear division, regulation of transcription,DNA-dependent, response to hormone stimuli and endoplasmic reticulum.

Network Inference using BioLayout

By conducting BioLayout analysis a total of 738 nodes, 7625 edges and 38 clusters were obtained for the interaction dataset containing the gene IDS for both cultured and uncultured datasets. Graphs were also generated in BioLayout that were showing the gene expression pattern in clusters. In the graphs, the genes which were more expressed had a peak whereas low expressed genes had a downward pattern in the graphs. Network was showing nodes and edges and clusters were representing the co-expressed genes in list form (Figure 2).

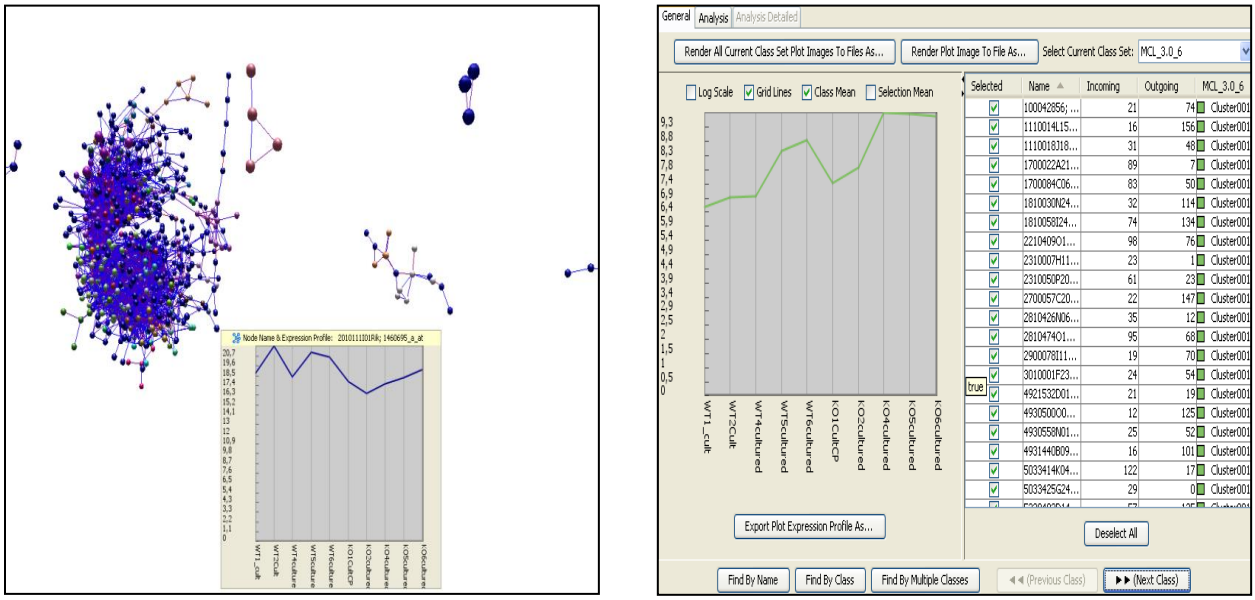

Figure 2: BioLayout, SnapShot. At left side, network snapshot in BioLayout, a main large network having nodes and edges is represented. At right side, a graph along with list of genes in form of cluster is shown.

Network Inference using GeneNet

GeneNet generated 148 nodes and 150 edges. The network file was loaded in to Cytoscape for making visualization and this generated information in form of network and cluster. In Cytoscape a big network was observed. The genes which were having the functional interactions with each other were in one network.

FUNCTIONAL ENRICHMENT STUDY FOR COMPARISON OF CULTURED AND FRESH DATASETS USING DAVID

Comparison of interaction dataset for BioLayout and GeneNet

Only two terms, "cytoplasm and cytoskeleton", were overlapped in all categories having a P-value less than 0.05 for the interaction dataset. The P-values for cytoskeleton and cytoplasm were 0.0047 and 0.035 in BioLayout, whereas in Gene Net they were 0.027 and 0.025, respectively. Similarly, it was also observed that there were different genes involved in same processes of both tools as it was observed in comparison of fresh and cultured dataset in BioLayout (Table 1&2).

BioLayout have the ability to make the large graphs along with hundreds of edges and nodes by using the pairwise Pearson correlation coefficients and by sophisticated layout algorithm. GeneNet, on the other hand, calculates the nodes and edges by partial correlation matrices and uses the Benjamini and Hochberg's approach (Benjamini and Hochberg's, 1995).

In GeneNet a very low number of edges and nodes are observed due the use of partial correlation measures because it calculates the linear correlation between two genes by removing the effect of any distinct correlation effect of any other genes. A higher number of edges and nodes are obtained in BioLayout due to the use of Pearson correlation which calculates the correlations among genes by even directing the indirect correlations of all other genes.

From the results it was obvious that general comparison of the cultured and uncultured data from the DAVID database without using the network approach revealed that there were significant functional categories like regulation of organelle organization, regulation of cell cycle, regulation of transcription, response to hormone stimulus etc. From previous literature it is clear that *SOCS2* have a major role in many pathways like regulation of growh hormones (Turnely, 2005), activation of transcription 5b target in liver (Vidal *et al*., 2007) and regulation of organization in the growing skeleton (Macrae*et al*., 2009) and in growth regulation (Greenhalghand, 2005) which supports our findings.

Table 1: Genes involved in cytoskeleton activity for both cultured and fresh dataset in Bio Layout and GeneNet

Genes involved in cytoskeleton activity in interaction dataset in Biolayout	Genes involved in cytoskeleton activity in interaction dataset in GeneNet
1 ADP-ribosylation factor-like 2 2- CDC42 effector protein (Rho GTPase binding) 1 3- Sfi1 homolog, spindle assembly associated (yeast). 4-centrosomal protein 164.	1- DNA methyltransferase 3B. 2- SMEK homolog 2, suppressor of mek1 (Dictyostelium). 3-centrosomal protein 250 4-pericentriolar material 1,

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Table 2: Genes involved in cytoplasm activity for both cultured and fresh dataset in Bio Layout and GeneNet

Genes involved in cytoplasm activity in interaction dataset in GeneNet	Genes involved in cytoplasm activity in interaction dataset in Biolayout
1 Aldehyde, dehydrogenase family 1 2- subfamily A2, RAN GTPase activating protein 1 3- RAN GTPase activating protein 1 4- RAN binding protein 17 5- ADP-ribosylation factor 3 6- progesterone receptor, testis-specific serine kinase 2 7- ring finger protein 17 8-retinoic acid induced 14	1- Threonyl-tRNAsynthetase-like 2 2- CDC42 effector protein (Rho GTPase binding) 1 3- centrosomal protein 250 3- annexin A6, centromere protein J 4- mindbomb homolog 2 (Drosophila) 5- rho/rac guanine nucleotide exchange factor (GEF) 18

CONCLUSION

Our findings showed that there were no significant common and overlapping functional categories when comparing the cultured and uncultured datasets. Different genes participating in bone growth were identified. Based on these findings it is suggested that useful biological information can be explored for studying genetical genomics by using different network tools. Still, more verifications and repetitions are needed to confirm these findings by using different combination of bioinformatics tools.

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