Identifying the Drug Targets in Metabolic Syndrome using Network Biology

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Abstract— The metabolic syndrome is a multiplex risk factor that consists of several risk factors such as heart diseases, hypertension, diabetes mellitus, cardiovascular diseases and so on. The prevalence of metabolic syndrome increases with age and varies with gender and ethnicity. Here, in this study we worked on three conditions that are associated with metabolic syndrome which includes Diabetes mellitus, Cardiovascular & Hypertension disease. To understand the diseases and its regulation, the primary role is to screen the genes involved in a particular condition. The differentially expressed genes including up regulation and down regulation are screened and extracted from Expression atlas, Cytoscape and Reactome FI database. The regulation of these extracted genes in a disease condition is analyzed and the disease network is generated. These disease networks may pave the way in understanding the pathophysiology of the diseases, for identifying biomarkers and in hubs analysis which may act as a potential drug targets in drug development industry.

Keywords: Metabolic Syndrome, Expression Atlas, Cytoscape, Reactome FI

I. INTRODUCTION

Metabolic syndrome is a cluster of conditions, which includes increased blood pressure, a high blood sugar level, excess body fat around the waist and abnormal cholesterol levels that occur together, increasing your risk of heart disease, stroke and diabetes.

Metabolic syndrome is also known as metabolic syndrome X, cardiometabolic syndrome, syndrome X, insulin resistance syndrome, Reaven's syndrome (named for Gerald Reaven), and CHAOS (in Australia).

Most of the disorders associated with metabolic syndrome have no symptoms, although a large waist circumference is a visible sign. If your blood sugar is very high, you might experience signs and symptoms of diabetes, including increased thirst and urination, fatigue, and blurred vision. The main sign of metabolic syndrome is central obesity (also known as visceral, male-pattern or apple-shaped adiposity), overweight with adipose tissue accumulation particularly around the waist and trunk. Other signs of metabolic syndrome include high blood pressure, decreased fasting serum HDL cholesterol, elevated fasting serum triglyceride level (VLDL triglyceride), impaired fasting glucose, insulin resistance, or Pre-diabetes. Here in this study we tried to focus on three diseases that are involved in metabolic syndrome which includes diabetes mellitus, hypertension and cardiovascular disease

A. Diabetes Mellitus

Diabetes is a problem with your body that causes blood glucose (sugar) levels to rise higher than normal. This is also called hyperglycemia [1].

B. Hypertension

Hypertension (HTN or HT), also known as high blood pressure or arterial hypertension, is a chronicmedical condition in which the blood pressure in the arteries is elevated. Hypertension is a major risk factor for hypertensive heart disease, coronary artery disease, stroke, aortic aneurysm, peripheral artery disease, and chronic kidney disease[2].

C. Cardiovascular Disease

Heart and blood vessel disease also called heart disease includes numerous problems, many of which are related to a process called atherosclerosis. Atherosclerosis is a condition that develops when a substance called plaque builds up in the walls of the arteries. This buildup narrows the arteries, making it harder for blood to flow through. If a blood clot forms, it can stop the blood flow. This can cause a heart attack or stroke [3].

II. MATERIAL & METHOD

A. Expression Atlas

The Expression Atlas provides information on gene expression patterns under different biological conditions such as a gene knock out, a plant treated with a compound, or in a particular organism part or cell. It includes both microarray and RNA-seq data. The data is re-analyzed in-house to detect interesting expression patterns under the conditions of the original experiment [4].

B. Cytoscape

Cytoscape is an open source software platform for visualizing molecular interaction networks and biological pathways and integrating these networks with annotations, gene expression profiles and other state data. Although Cytoscape was originally designed for biological research, now it is a general platform for complex network analysis and visualization [5].

C. Reactome FI

It is a database of core human pathways - DNA replication, transcription, translation, the cell cycle, metabolism, and signaling cascades - and can be browsed to retrieve up-to-date information about a topic of interest, e.g., the molecular details of the signaling cascade set off when the hormone insulin binds to its cell-surface receptor, or used as an analytical tool for the interpretation of large datasets like those generated by DNA microarray analysis. The information in Reactome is provided by expert biologists and gathered from the published research literature [6].

III. RESULT & DISCUSSION

A. Identification of Differentially Expressed Genes:

Hypertension, Diabetes mellitus, cardiovascular diseases term is searched in Expression atlas database for their differentially expressed genes such as up and down (Table 1)

Disease	Total no. of genes	Ups	Downs
Diabetes mellitus	**1581**	**689**	**892**
Hypertension	**189**	**35**	**154**
Cardiovascular	**1686**	**1384**	**302**

Table 1: shows the differentially expressed genes in diabetes mellitus, hypertension and Cardiovascular disease

B. Generating the Network for the Differentially Expressed Genes

The network for the differentially expressed genes is predicted using Reactome FI. The network of Hypertension generated contains 183 nodes & 608 edges. Similarly, the networks of Diabetes mellitus and Cardiovascular disease contain 183 nodes; 563 edges and 109 nodes; 239 edges (Table 2, Figure 1)

Disease	Nodes	Edges
Hypertension	**183**	**608**
Diabetes mellitus	**183**	**563**
Cardiovascular	**109**	**239**

Table 2: shows the information on the nodes and edges of the networks generated for diabetes mellitus, hypertension and Cardiovascular disease

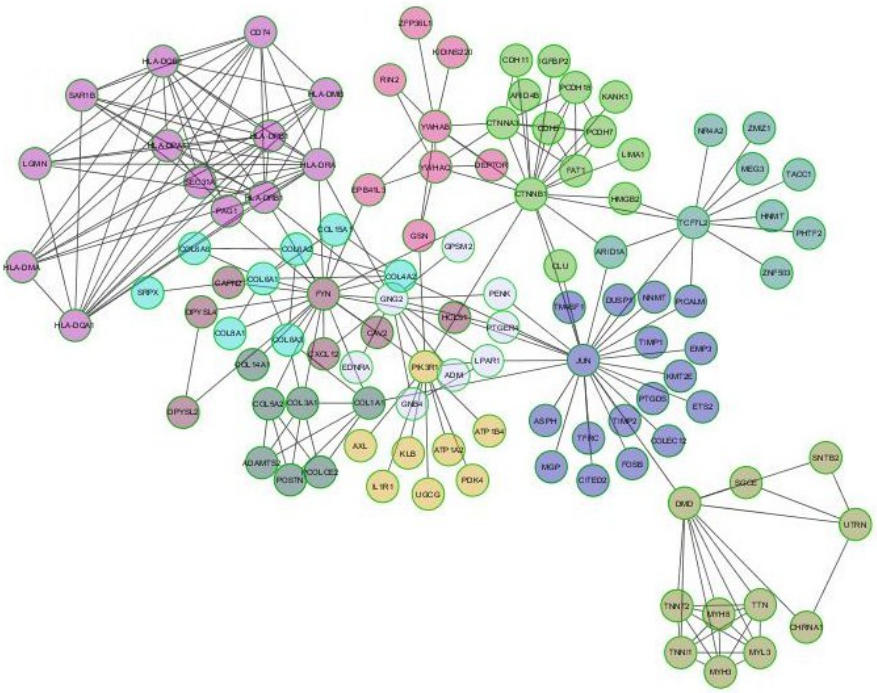

Fig. 1: shows the cardiovascular disease network generated for the differentially expressed genes

C. Identifying the Highly Connected Nodes in the Disease Network Predicted:

We identified the highly connected nodes through hub analysis for the Cardiovascular, Diabetes mellitus & Hypertension disease. The highly connected nodes for the Cardiovascular, Diabetes mellitus are manually checked by counting the number of nodes to particular genes which are mentioned in the Table 3. In hypertension, the number of highly connected nodes was vast where further analysis is to be done.

DISEASE	HUBS	Number of Links
Cardiovascular	1.DMD	10
	2.HLA-DPA1	12
	3.PIK3R1	13
	4.FYN	18

	5.JUN	27
Diabetes mellitus	1.UBC	Approx. 28
	2.EP300	Approx. 30
	3.NFKB1	Approx. 30
	4.MAPK3	Approx. 25

Table 3: Shows the top 5 highly connected node with the number of links

IV. CONCLUSION

In this work the differentially expressed genes in cardiovascular disease, diabetes mellitus and hypertension were screened and the disease networks based on human gene interaction were predicted for the differentially expressed genes obtained. The highly connected node is analyzed manually from this disease network which includes JUN (JUN proto-oncogene) for cardiovascular disease is 27, MAPK1 (Mitogen activated protein kinase) for diabetes mellitus is approx. 35.These networks may pave the way in understanding the pathophysiology of the diseases, for identifying biomarkers and in hubs analysis which may act as a potential drug targets in drug development industry.

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