

Article

## Investigation of common disease regulatory network for metabolic disorders: A bioinformatics approach

Tasnuba Jesmin<sup>1</sup>, Sajjad Waheed<sup>1</sup>, Abdullah-Al-Emran<sup>2</sup>

<sup>1</sup>Department of Information & Communication Technology, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh

<sup>2</sup>Department of Biotechnology and Genetic Engineering, Mawlana Bhashani Science and Technology University, Santosh, Tangail-1902, Bangladesh

Email: tasnuba\_it08005@yahoo.com

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### Abstract

Metabolic disorder causes the failure of metabolism process is growing concern worldwide. This research predicts a common metabolic pathway that is shared by Obesity, Type-2 Diabetes, Hypertension and Cardiovascular diseases due to metabolic disorder. A protein-protein interaction network is created to show the protein co-expression, co-regulations and interactions among gene and diseases. Genes whose are associated with metabolic diseases have been accumulated from different gene databases with verification and ‘mined’ them to establish gene interaction network models for expressing the molecular linkages among genes and diseases which affect disease progression. The number of associated genes identified for Type 2 Diabetes (T2D) is 250, Hypertension (HT) is 156, Obesity (OB) is 185 and cardiovascular disease (CVD) is 178. Among the sorted candidate gene 10 common genes are identified whose are directly or indirectly associated with four diseases by doing linkage filtering. By analysing the gene network model and PPI network a common metabolic pathway among metabolic diseases has been investigated.

**Key words** data mining; metabolic disorders; metabolic diseases; PPI network; gene regulatory network.

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### 1 Introduction

According to the WHO, overweight and obesity are among the five leading causes of deaths. Today 65% of the world's population live in countries where overweight and obesity are responsible for more deaths than underweight (World Health Organization, WHO) (World Diabetes, 2008). Overweight causes Obesity leads to death due to Type 2 diabetes, Hypertension, Cardiovascular diseases and other metabolic disorder diseases. Barness et al. (2007) reported that preventable cause of death worldwide is influenced by obesity where adults and children are becoming more affected, and very few public health problems of the 21st century are as

viewed awful as obesity. On average, life expectancy shorten by six to seven years as a consequence of obesity (Haslam and James, 2005; Peeters et al., 2003), life expectancy decreases by two to four years as a result of BMI of 30-35 kg/m<sup>2</sup>, while severe obesity (BMI > 40 kg/m<sup>2</sup>) reduces life expectancy by ten years what is proposed by another article (Whitlock et al., 2009). On the other hand there is a vital correlation between obesity and type-2 diabetes (K. Ahmed et al., 2012).

The increasing level of Type 2 diabetes may remain in undetected for many years. In 2014, 9% of adults 18 years and older had diabetes. In 2012 diabetes was the direct cause of 1.5 million deaths. More than 80% of diabetes deaths occur in low- and middle-income countries as like Bangladesh. Both lifestyle and genetic factors have a role to initiate type 2-diabetes (Ripsinet al., 2009; Riserus et al., 2009). So type-2 diabetes and metabolic disorder have a correlation. The authors Chobanian AV et al. proposed in their article at 2003 that hypertension is a chronic metabolic disorder. Kearney PM et al. proposed at 2005 that both developed (333 million) and undeveloped (639 million) countries hypertension are general. A prospective cohort study (Gress et al., 2000) proposed that T2D mellitus was almost 2.5 times higher to develop in subjects with hypertension compare with normal blood pressure. The article (Cheung, 2010) showed that there is a strong correlation between obesity and hypertension. They are proportionally increased or decreased.

In a multinational study, 50% of people with diabetes die of cardiovascular disease (primarily heart disease and stroke) (Morrish et al., 2001). Kvan et al. (2007) and Norhammar et al. (2004) also proposed that metabolic syndrome is a major risk factor to increase cardiovascular disease. Obesity and type 2 diabetes are responsible to initiate metabolic syndrome (Isomaa et al., 2001). Now cardiovascular diseases are usually connected with obesity and diabetes mellitus (Highlander and Shaw, 2010). Lastly obesity, type-2 diabetics and CVD are correlated. Disease genes cause or contribute genetically to the development of the most complex diseases. Gene alteration or their mechanical changes are mainly amenable to create disease. But for a particular disease gene or a set of genes play a major role. Those are called disease genes. Proteins are responsible for maintaining all cellular functions and their production is governed by the genetic code. A disease may be the result of gene abnormality that causes any kind of changes in protein function. Therefore, to establish network among gene it is very important to analyze the Characteristic of proteins and understanding their function.

Klingstrom and Plewczynski (2011) described about the different types of Bio Informatics tool that are helpful to show interaction, predict pathway and represent the interaction prediction among diseases, genes as well as proteins. Kanehisa et al. (2008) provided detail information about KEGG database use and analysis. Carretero and Oparil (2000) and Ashish Aneja et al. (2004) proposed that hypertension and obesity are strongly interconnected, even that obesity is the main factor of causing hypertension. This paper has vast description about hypertension and it stages. Type 2 diabetes and hypertension have common metabolic pathway during the genetic level, known from article (Bernard et al., 2012). Microvascular and macrovascular complications of diabetes are major causes of coronary heart diseases (CHD).The UNIHI tool what is used to predict PPI network and Common metabolic pathway is referred by Kalathur et al. (2014). At July 2014 a research paper has been published in Public health and proves that Adult obesity causes type-2 diabetes. Julien Dusonchet et al. (2014) have focused that type 2 diabetes leads the cause of cardiovascular disease.

Over the last few years, there has been a growing concern in the study of biological interaction networks at the genetic levels (Zeitoun et al., 2012; Rahman et al., 2013; Zhang, 2012; Zhang and Li, 2015). Identifying basic structural relationships among the diseases, gene and protein is the main goal in the field of gene regulatory interaction network. A community based approach gene regulatory network is established for complete or incomplete topology using genes (Meyer et al., 2014). The authors proposed that Gene regulatory networks (GRNs) regulate critical events during development of Cells (Wang et al., 2014). The paper

(Simoões-Costa et al., 2014) identifies new links in the gene regulatory network which is responsible for development of this critical cell population. They also provide unprecedented characterization of the migratory CNC transcriptome. Hayes and Dinkova-Kostova have designed an Nrf2 regulatory network. An interface between intermediary metabolism and redox can be gained through Nrf2 regulatory network. Julien Dusonchet et al. have designed a Parkinson's disease gene regulatory network and that is capable to find out LRRK2 gene regulatory network model.

A paper (Ville-Petteri Mäkinen, 2014) proposed a Gene Networks for Coronary Artery Disease with Molecular Pathways for Integrative Genomics. The paper has investigated the role of gene duplication for creating gene network evolution (Teichmann and Babu, 2014). Apostolos Zaravinos et al. showed that there is an associated network among deregulated genes for cohort of ccRCC tissues. They also suggest that these genes are candidate predictive markers of the disease (Apostolos Zaravinos et al., 2014). Medaa et al. proposed a genetic association's mode network for psychotic bipolar disorder and schizophrenia. A miRNA-TF-gene regulatory pathway in obesity is designed by Zhang et al. (2015).

Complex interactions among the cell's numerous constituents such as protein, DNA, RNA and other small molecules are responsible to create Biological functions. Thus, for it is important to assess interactions among gene-gene, gene-protein and metabolic levels. The presented research work has applied a system in bioinformatics approach for developing a gene interaction network model by taking high throughput genomic and PPI data for those diseases.

According to the above discussion on obesity, type-2 diabetics, hypertension, cardiovascular disease, it is visualized that they may be directly or indirectly interconnected with metabolic disorder. But is any common pathway shared by obesity, type-2 diabetics, hypertension, and cardiovascular disease? The investigation procedure and result is discussed in section 2 and 3 respectively.

## 2 Materials and Methods

There are some steps to accomplish a gene network topology which aids to establish a common pathway. Step by step details description is shown below subsections through 2.1 to 2.2.7 respectively.

### 2.1 Data source

For the purpose of this research genes associated with Type 2 Diabetes, Hypertension, obesity and Cardiovascular diseases are collected from PubMed. PubMed is the reliable and authentic storage for different kind of genetic data. Those sources of PubMed are maintained by the NCBI (National Center of Biotechnology Information). The NCBI is freely accessible and downloadable gene database. GENE Bank data warehouse and OMIM database are also used to collect the gene list for T2D, CVD, OB and HT.

### 2.2 Methods

#### 2.2.1 Gene integration and processed

In this study, the disease genes are defined as the reported genes provided by the NCBI. The NCBI provides a quality-controlled and literature-derived collection. The candidate genes are enlisted according to the specific disease and merged the collected genes for each disease.

The collected genes are also verified using KEGG database. KEGG database resource consists of the sixteen main databases. They are broadly categorized into systems information, genomic information and chemical information and further subcategorized by color coding of web pages. KEGG pathway contains around three lakhs entries for pathway maps built from around five hundreds manually drawn diagrams. After the collection and integration the merged gene lists for each disease are processed individually to avoid duplication and unnecessary genomic data.

### 2.2.2 Gene mining

Data mining is mainly used for making data appropriate for analysis and application. The listed candidate genes related to the type-2 diabetes, obesity and hypertension and cardiovascular disease has been mined according to metabolic disorder by using data mining technique and stored in Unigene data warehouse. Unigene is primarily a database in NCBI. But it refers to cluster of genes that perform a particular function. Due to the application of mining technique on gene this step is named as Gene Mining.

### 2.2.3 Gene identification according to disease

To identify the interrelated genes among metabolic diseases there is used EXPASY database which help to find out genes those are not only related to diseases also have action for the cause of crashing metabolism process of specific diseases.

### 2.2.4 Gene sorting

Sorting is the most crucial part of this research because any kind of tinny mistakes can remove the important gene that may give wrong result. Sorting algorithm of Taxonomy database is used here to sort the identified genes whose are internally correlated among obesity, T2D, hypertension and cardiovascular disease. The common gene among theses 4 diseases has been determined those are directly or indirectly affect the each disease.

### 2.2.5 Gene filtering

This is the critical step of this research and here is used UniHi tool. UniHI (Unified Human Interactome) is an Omic tool Linkage Network filtering Technique is used to identify the common gene within the target diseases T2D, OB, HT and CVD. UniHi tool is applied to find out those genes that have minimum binary and also complex interaction among themselves. The investigated common genes are used to establish a PPI network.

### 2.2.6 PPI network creation

Protein-Protein interaction network plays an important role in bioinformatics research. PPI network also helps to understand about the molecular mechanism of human diseases signaling pathways and to identify a new module of disease processes. UniHi is now a very popular reliable bioinformatics tools to represent PPI maps among genes. UniHI 7 currently includes almost 350 000 molecular interactions between genes, proteins and drugs, as well as numerous other types of data such as gene expression and functional annotation. Finally PPI network is created for common genes using UniHi tool.

### 2.2.7 Common regulatory pathway

Eight and final step is the construction of the common gene regulatory pathway. The common genes among these diseases are verified with KEGG database in different biological pathways. The selected genes are cross-validated and clustered using the KEGG mining tools (Kanehisa et al., 2008). From the pathway information on the selected genes, there have predict common regulatory pathway using UniHI.

## 3 Results

A disease is rarely a consequence of an abnormality in a single gene directly, there are the effect of more than one gene directly, indirectly even through proteomic level. The Different Bioinformatics tools establish a new way to analysis the disease process by using gene and protein structure and interaction among themselves. The trustable gene database permits free access to collect genetic data related to specific disease and the tools advances the old version treatment by representing the deep level of genetic abnormality.

### 3.1 Gene collection, integration, mining and sorting

Collected responsible genes for target diseases (T2D, HT, OB and CVD) from PubMed, OMIM and Gene bank database are merged and processed. The result shows responsible genes for T2D is 2794, HT is 1520, OB is 2531 and CVD is 4713. Unigene Database is used here to mine the processed list of responsible gene. After

mining the responsible genes are reduced for each disease. The resultant responsible genes are now for T2D, HT, OB and CVD are 250,156, 185 and 178 respectively. Table 1 shows the full description of resultant responsible genes history of each sector. Among them the candidate genes are selected those are connected with any one of the above mentioned diseases. The candidate genes are justified experimentally using KEGG pathways. After analyzing the result the genes are picked out for T2D is 125, HT is 121, OB is 108 and CVD is 110. After passing the sorting stage the number of genes identified for Type 2 Diabetes, Hypertension, Obesity, Cardiovascular diseases are 62 genes.

**Table 1** Gene Collection chart for metabolic disorder and target disease according to Homo sapiens

Name of Disease	Primary Number of Gene Collection	Gene No. for Metabolic Disorder	Gene No. for human and Metabolic Disorder
Cardiovascular Disease	4713	208	178
Obesity	2531	222	185
Type2 Diabetes	2794	298	250
Hypertension	1520	191	156

### 3.2 Gene linkage filtering among T2D, OB, HT and CVD

Cross linkage is used here to investigate the molecular cross-talk within four interrelated diseases (like T2D, HT, OB and CVD) mechanisms. The results of every cross linkage are shown in Table-2. The individual disease networks were looked thoroughly at their 'hubs'. Analysis of the gene patterns and their relatedness within different diseases is down to collect genes of four diseases. Through the investigation of connecting procedure and cross talk, a gene list is generated. The gene list contains all types of connections among four diseases. During this process the common genes for all four diseases is found 10. These genes are NR3C1, APOA1, APOB, CCL2, IL6, STAT3, NFKB1, LPL, PPARGC1A and TNF.

**Table 2** Cross Linkage gene chart for metabolic disorder and target disease according to *Homo sapiens*.

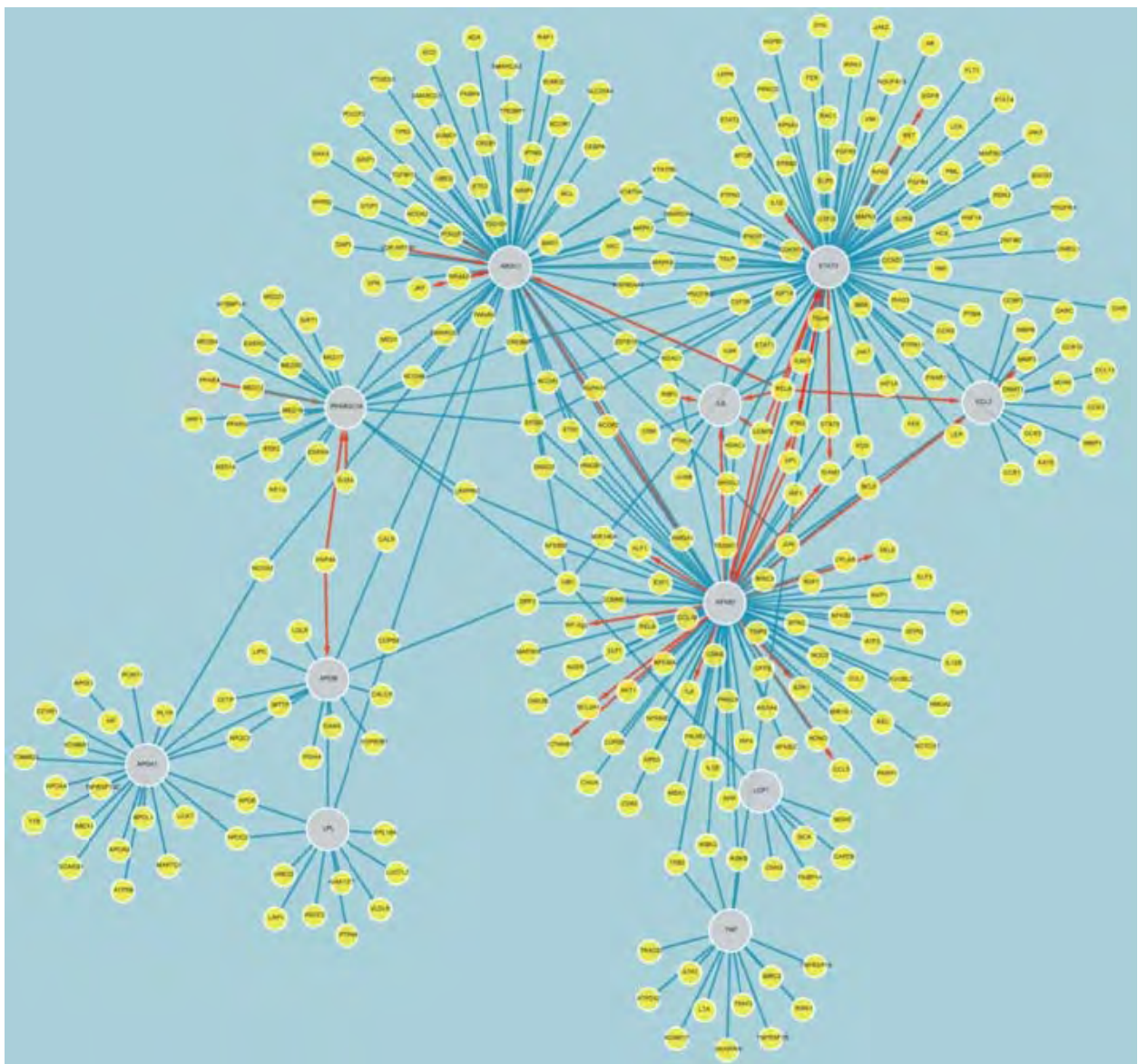
Cross Linkage Between	No of Gene	Cross Linkage Among	No. of Gene	Common Gene No.
CVD and OBS	110	CVD, OBS and HT	108	62
CVD and T2D	125	CVD, OBS and T2D	92	
CVD and HT	108	OBS, T2D and HT	88	
OBS and T2D	136	CVD, T2D and HT	90	
OBS and HT	98	CVD, OBS, T2D and HT	70	
T2D and HT	121			

### 3.3 PPI network among common genes

After analyzing the background studies one Omic bioinformatics tool is selected to go ahead of this research called UniHI. UniHI can represent the protein-protein interaction network pattern among the candidate gene. The PPI network around common genes is given in Fig. 1. PPI network represents the relationship among genes and hub protein. Some genes are connected with each other directly and some are connected via another gene or hub protein. Gene regulatory model of each common gene is also given in Fig. 1.

### 3.4 Common regulatory pathway

To identify the common regulatory pathway among common candidate gene there is used three steps for confirmation. Common regulatory pathway for each hub genes are determined, any pathway that is common at least two hub genes.



**Fig. 1** PPI network among common genes represents the common regulatory pathway.

### 3.4.1 Step-1: relationship among common genes

Common regulatory pathway around the common genes is outlined by UniHI in Figure-1. The RELA connects the Candidate genes STAT3, NFKB1, CCL2, NR3C1 and IL6. NFKB1 also directly connected with SP1 and CEPBP. NFKB1 is directly connected with IL6, CC12 and NR3C1. NFKB1 and TNF are connected indirectly by TAB2, IKBKB and IKBKG. PPARGC1A has direct connection with APOB through HNF4A. Again APOB has indirect connection with both APOA1 and LPL. LCP1 gene keeps the indirect communication using UBC with NR3C1, NFKB1, STAT3, APOB and PPARGC1A.

### 3.4.2 Step-2: result validation of step-1 using GeneMANIA

By using GeneMANIA tools there is identified the pathway among those candidate gene which gives almost same result as like step 1. A network is also generated with common metabolic pathway. NFKB1 connects five genes CCL2, NR3C1, TNF, STAT3 and IL6. STAT3 has connection with LPL and LPL has connection with APOB and both APOB and APOA1 has interrelationship. So the common pathway among NR3C1, APOA1, APOB, CCL2, IL6, STAT3, NFKB1, LPL, PPARGC1A, TNF genes maintained in a cycle as like APOA1-APOB-LPL-PPARGC1A-STAT3-TNF-NFKB1-CCL2-NR3C1-IL6.

### 3.4.3 Step-3: result validation of step-1 using UNIHI

The result of UNIHI tool is more specified. Among NR3C1, APOA1, APOB, CCL2, IL6, STAT3, NFKB1, LPL, PPARGC1A, TNF genes the common metabolic pathway cycle covers NFKB1-PPARGC1A genes. Each of these hub genes is connected to other candidate gene and keeps effect on the expression of responsible gene. The result of every step in subsection 3.4.2 provides the same metabolic pathway. That validates the proposed common metabolic pathway among T2D, OB, HT and CVD disease.

## 4 Discussion

Studies on the functional cross-links between gene associated diseases and specific disease are still in their early stages and not well known much. Understanding the genetic mechanisms of diseases it is important to know and analyze the Connections between genes and diseases. Both Candidate genes associated with Type-2 Diabetes, Hypertension, Cardiovascular disease, obesity and the metabolic diseases are topologically important to construct a metabolic diseases network. Via mapping inter-genes to PPI, show the association among the selected diseases through the genetic level there is constructed a cross talking sub pathway. A cross-talking sub pathways network analysis gives a great performance capturing higher-level relationship among gene and disease. The network-based analysis provides a rather than promising insight of a common metabolic path between gene and disease.

Type-2 Diabetes, Obesity, Hypertension and Cardiovascular diseases cause due to the abnormality of metabolism. To identify the interrelationship among these metabolic diseases have selected the genes related to the diseases those have perfect biological relation to the specific disease. Cross linkage among metabolic disease shows the relationship among them through gene level. Selection of a good set of gene can represent an accurate Protein-Protein Interaction network among diseases and diseases genes. By mapping and analyzing the PPI network common metabolic path has been investigated. By this Common metabolic pathway there is established a metabolic diseases network which can regulate the expression of gene. This research is mainly helpful to understand the metabolism network among genes and to target drug design

## Abbreviations

T2D=Type-2 Diabetes; OB=Obesity; HT= Hypertension; CVD=Cardiovascular Disease

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