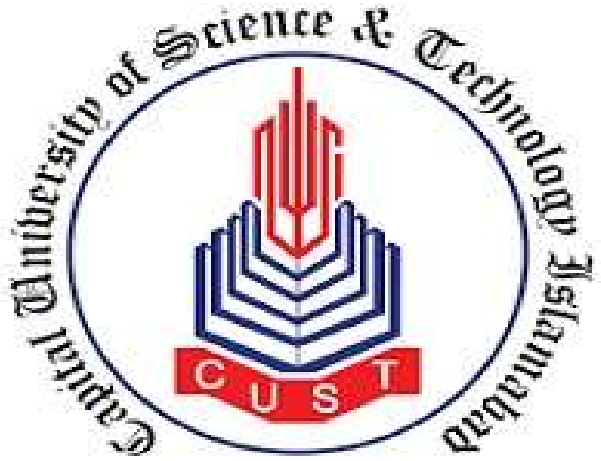
Impact Estimation of inflammatory gene IL-6, TNF-alpha and ACE on diabetes and obesity as co-morbidity of CAD

By

Muhammad Nadeem

MASTER OF SCIENCE IN BIOINFORMATICS



DEPARTMENT OF BIOSCIENCES
Capital University of Science and Technology
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2017

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MUHAMMAD NADEEM

A research thesis submitted to the Department of Biosciences,
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Declaration

I am here declaring that, the content provided in this thesis is my own original work, except where otherwise acknowledged, All the information presented here with material is original. I have not presented any part of this research elsewhere for any other degree previously.

Muhammad Nadeem

Dedication

I am dedicating this thesis to my beloved parents, who's taught me best to believe on Allah Almighty and himself. It also dedicated to my sisters, who taught me how to passionate and controls emotions. I am also dedicating this work to Uffaq Naz, Syed Ahtisham Zulfiqar Ali Naqvi and my best friend Raja Adeel Hussain, for encouraging me all the way.

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Definitions, Acronyms, and Abbreviations

CAD	Coronary Artery Disease
LCA	Left Coronary Artery Disease
RCA	Right Coronary Artery Disease
LAD	Left Anterior Descending Artery
LCx	Left Circumflex
PAD	Posterior Descending Artery
VSMC	Vascular Smooth Muscle Cell
NCD	Non-Communicable Complex Disease
CVD	Cardiovascular Disease
CHD	Coronary Heart Disease
MI	Myocardial Infraction
DM	Diabetes Mellitus
IDDM	Insulin Dependent Diabetes Mellitus
NIDDM	Non Insulin Dependent Diabetes Mellitus
IL-6	Interleukin-6
ACE	Angiotensin Converting Enzyme
TNF-α	Tumor Narcosis Factor Alpha
HGP	Human Genome Project
GWAS	Genome wise Association Studies
SNPs	Single Nucleotide Polymorphism

AHA	American Heart Association
IDF	International Diabetes Federation
BMI	Body Mass Index

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In the name of Allah, The most beneficent, the most Merciful, All praises to Almighty Allah;
Who's blessed me with enthusiasm, strength of mind, and courage to complete entire task. I am thankful to him because I am belonging to Muslim ummah of his Last prophet Mohammad (peace be upon him) due to his mercy.
The entire research was performed in Capital university of Science and Technology, Islamabad, Pakistan. I am thankful to university for providing me lab facilities.
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In the end, I would like to say thanks to **all** those peoples who prayed for me. I am also expressing my apology to those, whom I could not mention personally one by one.

Muhammad Nadeem

ABSTRACT

Coronary Artery Disease is abnormality of coronary artery which supplies blood to heart. It is non-communicable complex disease with numerous causes. Genetic as well as environmental reasons are reported to be involved in causing coronary artery disease. Risk factors include hypertension, obesity, diabetes, smoking, cholesterol, fats, physical inactivity and Inflammation. Inflammatory marker IL-6, ACE and TNF-alpha play a vital role in on set of coronary artery diseases. These inflammatory markers reported from various population and diseases such as obesity, diabetes and hypertension. This project was designed co morbidity diabetes, coronary artery disease and obesity disease because of genetic variation of interleukin-6, Angiotensin Enzyme and tumor necrosis factor alpha. All these inflammation inducing genes are reported to cause these diseases individually. Pathways enrichment method was explained to identify the role of inflammatory genes in causing obesity, diabetes and coronary artery disease simultaneously. The results were verified and analyzed using protien-protien interaction network and disease-Gene network analysis. Coronary artery disease, obesity and Diabetes are linked and associated with each other through AGE/RAGE and HIF-1 Signaling pathway. It was also found that TNF is the common inflammatory genetic cause responsible for coronary artery disease and Obesity and Diabetes. Therefore, AGE/RAGE pathway could be an important drug target and provides bases for precision medicine.

CHAPTER 1

INTRODUCTION

Coronary Artery disease (CAD) is abnormality of coronary artery which supplies blood to heart. Coronary arteries are of two fundamental types, right coronary artery (RCA) and left coronary artery (LCA). Left anterior descending artery (LAD) and the circumflex (LCx) are two sub-branches of left coronary artery. These are providing supply of blood to left side and Lateral side of heart respectively. Right coronary artery (RCA) split into the posterior descending artery (PDA) and acute marginal arteries later on. These provides blood to right ventricle, Ventricular hub and variable area of the left ventricle (RO, Mann, Zipes, & Bonow, 2008). CAD is result of blockage in inner wall of arteries. The blockage could be due to plaque formation or coagulation in artery which is known as atherosclerosis. It blocks the supply of blood to heart and other body parts, which leads to chest pain, ischemia, high blood pressure, heart failure, stoke and death (Lüscher, 2015). The Researches are being cared out to explain the underlying phenomena of the beginning, development and break of the coronary atherosclerotic plaque (Kume, 2010). These researches focused on investigated reasons for CAD, such as lipoprotein retention, vascular smooth muscle cell (VSMC) proliferation, endothelial dysfunction, lipid absorption by macrophage, platelet activation, and Thrombosis, inflammation response of the artery (Bui, Prempeh, & Wilensky, 2009; Fishbein, 2010).

It is non-communicable complex disease (NCD) with multiple factors involvement. It has environmental as well as genetic involvement in its complexity. Many other risk factors that take part in CAD disease include modifiable risk factors and non-modifiable risk factor. Modifiable risk factors comprise hypertension, obesity, diabetes, smoking, cholesterol, fats and physical inactiveness. Non-modifiable risk factor comprises of socioeconomic behavior, age, gender and family history etc (Lluís-Ganella, Lucas, Subirana, & Sentí, 2010; Roberts & Stewart, 2012; Tanuseputro, Manuel, & Leung, 2003). The Leading death causing disease around the world, which belongs to cardiovascular diseases (CVD) group is Coronary artery disease (CAD) (Hansson, 2005)

and its major mortality causing disease as well (Sasidhar, Reddy, Naik, & Naik, 2014). It is number one death killer in whole world. Thusly, about 1 in 7 adults in the united states are currently considered to be at high CV risk, with a >30% shot of creating coronary illness (Mozaffarian, Benjamin, Go, & Arnett, 2016). As indicated by one study in the vicinity of 18% and 23% of men and ladies pass on inside 1 year of having an underlying myocardial infarction (MI), while 18% to 35% of patients create repetitive dead tissue and 7% to 30% experience the ill effects of symptomatic heart distress (Velagaleti, Pencina, Murabito, & Wang, 2008).

Diabetes mellitus (DM) is inadequacy of the pancreatic hormone insulin, which brings about an inability to utilize sugars and starch. It is a chronic progressive metabolic disorder characterized by hyperglycemia. It has variety symptom, for example thirst, blurring of vision and weight reduction. The long term impacts of diabetes mellitus incorporate progressive growth of the specific complications like potential blindness, or renal failure (DeFronzo, Ferrannini, Zimmet, & Alberti, 2015).

It could harms to other organs like heart, eyes, kidney and veins. Person having diabetes had an expanded event of atherosclerotic cardiovascular, peripheral arterial and cerebrovascular diseases. Hypertension and lipoprotein anomalies processing are habitually found in individuals with diabetes. Numerous methods are incorporated into the progression of diabetes, as invulnerable framework destruction of the pancreatic β-cells in like manner of insulin deficiency, mall functioning in fat, carbohydrates and protein metabolism in diabetes make deficiency in insulin action on target tissues and inadequate insulin secretion or production in response of hormonal pathways (Zucchi, Ferrari, & Spina, 2004).

Diabetes is either due to not enough production of insulin by pancreas or body cells not properly responding to insulin production. It is separated in to two most important types, insulin dependent diabetes mellitus or IDDM (type I) and non insulin dependent diabetes mellitus or NIDDM (type II). Both are heterogeneous diseases. Type I diabetes is β-cells disruption which leading to absolute insulin deficiency and mostly in children only 5-10 percent in the world population. Type II diabetes is a progressive loss of insulin secretion

and mostly in adults with 90-95 percent in the whole world population (Association, 2016; Khodaeian & Enayati, 2015; Shomali, Montazeri, & Akrami, 2007). It is non-communicable complex disease with multiple factors involvement. It has environmental as well as genetic involvement in its complexity. Many other risk factors that take part in DM disease include modifiable risk factors and non-modifiable risk factor. Modifiable risk factors comprise hypertension, obesity, inflammation, Coronary artery disease, smoking, cholesterol, fats and physical inactiveness. Non-modifiable risk factor comprises of socioeconomic behavior, age, gender and family history etc (Khodaeian & Enayati, 2015; Yau, Rogers, & Kawasaki, 2012).

Diabetes is one of the most broadly occurring human diseases and the worldwide progression has risen over the past two decades. It turns into a plague which is not controlled like other real disease, for instance, malignancy and cardiovascular sicknesses, and winds up apparently 6th driving reason for death around the world. It is assessed that 415 million individuals had DM in 2015; by 2040 this would have ascended to 642 million (Marso & Daniels, 2016).

Obesity is a medical condition with excess amount of body fats accumulation. It may or may not have a negative effect on health. Its negative effects lead to reduce life expeptancey or increase health problems. It increases the ocurence of many diseases especially heart diseaeses, type 2 diabetes, obstructive sleep apenea and certain type of cancer (Channa & Saroor, 2015). It is a complex diseases heaving both environmental and genetic factors. It is multifactor heterogeneous condition due to complex interaction of genetic, behavioral and developmental factors (S & D, 2016). It is non-communicable complex disease with multiple factors involvement. It has environmental as well as genetic involvement in its complexity. Many other risk factors that take part in obesity disease include modifiable risk factors and non-modifiable risk factor. Modifiable risk factor comprises of hypertension, DM, Coronary artery disease, smoking, inflammation, cholesterol, fats and physical inactiveness. Non-modifiable risk factor comprises of socioeconomic behavior, age, gender and family history etc (S. Ng, Zaghloul, Ali, & Harrison, 2011).

Data mining is extraction of information from the raw data. Its techniques are highly applicable in field of bioinformatics since from the last decade (Kropp & Caulfield, 2004). In literature text mining technique data gathered from source and it processed with query keyword than according to desired literature, it has been extracted from data (Mathiak & Eckstein, 2004). Data mining is field which produces rapid advancements. The problem of text mining has increased attentions science from the last decade because Large text data availability on web. Information retrieval from data is always remaining preference of researches (Han, Pei, & Kamber, 2011).

Text Mining (TM) is type of Data mining procedure. It is used to mine information from not-structured or semi-structured data. It is also known as text data mining, which refers the process of deriving high-quality information from text. TM retrieves pattern within the structured data, assess them and finally produces the output (Agrawal & Batra, 2013a). TM helps biologists to mine information from a vast text in biomedical research (Zhu, Patumcharoenpol, Zhang, & Yang, 2013). Text mining process mostly divided into different sub steps likes Text summarization, Document Retrieval, Information retrieval, Assessing document similarity and Text categorization (Agrawal & Batra, 2013a).

Many studies have shown that CAD is based upon various features, such as inflammation causing genes, smoking, hypertension, gender, age, obesity and diabetes (Sayols-Baixeras, Lluís-Ganella, & Lucas, 2014; Yiannakouris, Katsoulis, & Trichopoulou, 2014; Yu, Zhang, Xiang, Yang, & Li, 2014). Hallmark of CAD is inflammation (Aprahamian & Sam, 2011; Kampoli, Tousoulis, & Antoniades, 2009; Libby, Ridker, & Hansson, 2009). It causes atherosclerosis in which immune responses generated with metabolic risk factors and then activation of plaque formation or coagulation in artery wall occurred (Hansson, 2005; Libby & Theroux, 2005). Inflammatory cytokines played vital role in Coronary artery disease (Goodwin, Pendleton, & Levy, 2007) obesity (Kiefer, Zeyda, Todoric, & Huber, 2008) and diabetes mellitus (Farah & Shurtz-Swirski, 2008). Inflammation pathogenesis of diseases played vital role and inflammatory markers like interleukin-6 gene (IL-6) (Satti, Hussain, & Javed, 2013), tumor narcosis factor Alpha

(TNF-α) (Kolb & Mandrup-Poulsen, 2005) and Angiotensin converting enzyme (ACE) (D. Ng, Tai, Koh, Tan, & Chia, 2005) cause these diseases.

These three are Non-communicable, inflammatory and complex disease with multifactor as concerning to environment as well as genetics. Genetic complexity factor involvement in CAD suggested that genes have role in causality. Many genes and SNPs are involved in causing the CAD has been reported in different population. Since from the last few decades with advent of human genome project (HGP), Genome wise association studies (GWAS), linkage analysis and correlation studies showed genes and single nucleotide polymorphism (SNPs) played vital role in CAD (Burton et al., 2007; Nair, Ghatge, Kakkar, & Shanker, 2014). Some of these genes are causing inflammation and has been used as inflammatory markers in different population studies. Some of these inflammation causing genes which are going to be studied in this research are ACE, IL-6 and TNF-alpha. These genes also involved in inflammation causing other diseases as obesity, diabetes, hypertension and arthritis etc.

Aims and Objectives

Inflammatory marker IL-6, ACE and TNF-alpha are playing a vital role in coronary artery diseases. These inflammatory markers were studied for different populations of diseases like obesity, diabetes and hypertension etc. The co-morbid effect of these genes which related to obesity, diabetes and hypertension had not studied yet in context of system biology. This study aims to study co-morbid effect of obesity, diabetes and CAD diseases with genetic variation of IL-6, ACE and TNF-alpha with the help of bioinformatics and system biology.

The objectives of this Study are:

- Selection/ Identification of Candidate genes involved in causing Diabetes, Obesity and CAD in co-morbid behavior.
- Construction of PPIs network of Candidate gene.
- Selection and functional analysis of hub genes in co morbidity conditions.

CHAPTER 2

LITERATURE REVIEW

Coronary artery disease is the leading cause of death in the world, characterized by the presence of atherosclerotic plaque in epicardial coronary arteries (C. K. Glass & Witztum, 2001). Also, CAD has been considered as the disorder of lipid deposition in the arteries (Bernhagen, Krohn, Lue, & Gregory, 2007). It has been accepted as an inflammatory condition due to the presence of pro-inflammatory biomarkers (Reilly, Lehrke, Wolfe, Rohatgi, & Lazar, 2005). CAD role with co-morbidity as diseases obesity and diabetes has been addressed from many studies. First of all, these are diseases follow Mendelian inheritance and only one gene could be responsible for disease occurrence in affected member of family. These are complex, non-communicable and inflammation causing diseases. These diseases have genetic and environmental factors and called multifactor diseases with other modifiable and non-modifiable risk factors. Modifiable risk factor of coronary artery disease comprises of hypertension, DM, obesity, smoking, inflammation, cholesterol, fats and physical inactiveness. Non-modifiable risk factor comprises of socioeconomic behavior, age, gender and family history etc and vice versa. These are the perplexing conditions, happening from a more extended timeframe and prompting high death rates. These are also considered as metabolic syndromes in the world.

Prevalence of diseases

Coronary artery disease (CAD)

Coronary artery disease (CAD) varies as prevalence in around the globe of world. It has different prevalence's in various regions of world. It is evaluated in 2010 that 16.5 million individuals passed on because of CVD round the world. Out of these, 7.2 million passing's happened because of CAD and 5.7 million individuals passed on from stroke (Lloyd-Jones, Adams, & Brown, 2010). According to American heart association (AHA) statistics 2016, around 1 in 7 grown-ups in the united states have high CV chance, with a >30% opportunity about Creating coronary disease (CHD) (Mozaffarian, Benjamin, Go,

& Arnett, 2016). The prevalence of coronary heart disease is high in Africa and the Middle East countries (Almahmeed, Arnaout, & Chettaoui, 2012).

Asians are considered to have high frequency of CVD occasions and the illness difficulties prompt expanded mortality in their population. They have more prominent weakness to CAD with more serious and unfavorable results when contrasted with the American and European populations, because of high risk factor density called "south Asian paradox" (Lloyd-Jones, Hong, Labarthe, & Mozaffarian, 2010). Happening of premature CAD in males and females of Pakistani population is 27.2% and 49.1% respectively (Kayani, Bakht, Munir, & Abid, 2011).

Diabetes Mellitus (DM)

Diabetes mellitus (DM) has a place with one of most seasoned diseases known to man. It was first detailed in Egyptian composition around 3000 years prior (Ahmed, 2002). In 1936, the distinction between type 1 and type 2 DM was clearly made (http: //science.jrank.org/pages/2044/Diabetes-Mellitus.html). Type 2 DM was first portrayed as a part of metabolic disorder in 1988 (Patlak, 2002). In 2010, it is estimated that 285 million people had diabetes around the world. About 90 percent belongs to type 2 DM. Projected number for 2030 of diabetes may rise to 439 million (Shaw, Sicree, & Zimmet, 2010). According to global burden disease report of 2011 it is assessed that 366 million individuals had diabetes in 2011. It might ascend in 2030 up to 552 million. It causes 4.6 million deaths in 2011 around the world (Whiting, Guariguata, Weil, & Shaw, 2011). The most recent worldwide estimate from the International Diabetes Federation (IDF) is that in 2015 there were 415 million individuals with diabetes mellitus and that by 2040 the number will be 642 million (http://www.diabetesatlas.org(2016)). Among the 10 nations with the biggest quantities of individuals anticipated to have diabetes mellitus in 2030, five are in Asia (China, India, Pakistan, Indonesia and Bangladesh) (Shaw, Sicree, & Zimmet, 2010).

Obesity

The expanding predominance of overweight and corpulence is a developing concern in most regions of the world. Late estimates bring demonstrated that the joined predominance of overweight and obesity among adults internationally has ascended by 28% over the most recent three decades, with 37% of males and 38% of females having a body mass index (BMI) of 25 kg m−2 or more prominent. From 2008 to 2013, the worldwide pervasiveness of overweight and obesity among youngsters 2–19 years expanded by 47 % (M. Ng, Fleming, Robinson, Thomson, & Graetz, 2014). The general predominance of overweight was 27.1% of the aggregate population and a high pervasiveness of overweight were observed in more seasoned females. The prevalence of obesity in females was higher (27.8%) than in males (10.6%)).

In females, weight was most surprising in the age bunch 45–64 years. The predominance of obesity in females demonstrated an expanding pattern from 13.6% in age bunch 15–25 years to 41.9% in age aggregate 55–64 year (Maimela, Alberts, Modjadji, & Choma, 2016). Central obesity is more prevalent amongst South Asians compared to Europeans (Misra & Khurana, 2011). Obesity is an expanding issue internationally. There is a thought that its pervasiveness is likewise expanding quickly in Asian nations (Koh, Loo, Goh, & Sugano, 2016). The joined rough overweight and obesity predominance gone from 5% in India to 60% in Australia. In spite of the fact that the total pervasiveness of overweight and weight in Australia is presently a few times that of China and Japan, the relative increments in frequency of overweight and obese in the course of the last 20 years in these two Asian nations have been huge (Jiao, Xu, Zhang, & Han, 2015).

Risk factor of diseases

A danger element alternately danger creator is any trait, trademark alternately presentation about a unique that increments the probability about Creating a sickness (Yusuf & Ôunpuu, 2001). CAD, obesity and diabetes are non-communicable complex disease with multifactor involvement in causing disease. These factors are differentiated into two types: modifiable and non-modifiable risk factors.

Modifiable risk factor

Common modifiable risk factor associated with these diseases includes hypertension, cholesterol, abnormal lipids, smoking, physical inactiveness and inflammation (Sayols-Baixeras et al., 2014; Yiannakouris et al., 2014; Yu et al., 2014). Obesity and diabetes mellitus are also modifiable risk factor of CAD and vice versa (Zucchi, Ferrari, & Spina, 2004). Body mass index, diet, hyperglycemia and insulin production are associated with obesity and diabetes (M. Ng, Fleming, Robinson, Thomson, & Graetz, 2014).

Hypertension principally ascribes to CAD and it raises the rate of early mortality around the globe (Vasan, Larson, Leip, & Evans, 2001). It is an important modifiable hazard factor, and clinical trials have shown that productive decrease of raised blood pressure to target levels converts into reduce chance for the progression of coronary artery disease, stroke, heart failure, and renal failure (Liao & Farmer, 2014). Obesity increases hypertension and known to involved in development of long term consequences of T2DM (Colosia, Palencia, & Khan, 2013). It is also an important factor for essential hypertension, diabetes, and other co-morbid conditions that contribute to development of diseases (Hall et al., 2014). Low-density lipoprotein (LDL) is vital conveying protein for total cholesterol in blood has been concerned in the progression of CAD (O'Donnell & Elosua, 2008). Smoking is an outstanding preventable risk factor in the progression of atherosclerotic occasions in young fellows and ladies. In early time of life, tobacco smoking contributes up to 40% passing rate in patients with basic complexities of heart disease, stroke, and vascular disease (Chen, Wang, Boeg, & Xia, 2002). Another most common risk factor is physical activity (Mayer, Erdmann, & Schunkert, 2007), Which reduced the risk of cardiovascular disease (Oguma & Shinoda-Tagawa, 2004).

Non-Modifiable risk factor

Common Non- modifiable risk associated with these diseases include age, sex, ethnicity and family history (S. Ng et al., 2011). Age and gender have higher influences upon these diseases with familial history regarding to different ethnic groups of the world. Relatives share qualities, way of life, and natural hazard calculates that on the whole contribute CAD onset (Mayer et al., 2007). CAD is an epidemic problem of all populations. South

Asians have greater occurrence of cardiovascular events as contrast to other populations (Forouhi, Sattar, Tillin, & McKeigue, 2006). Ethnicity is an important risk factor of CAD which affects the disease through dynamic and complex interactions of other associated risk factors (Rambihar, Rambihar, & Rambihar, 2010). Conventional risk factors like smoking, diabetes mellitus, lipids, and hypertension varies among sub-ethnic groups of south Asia (Forouhi et al., 2006). Family members share genes, lifestyle, and environmental risk factors that collectively contribute in CAD onset (Mayer et al., 2007). People, who have CAD patient as a close family member, are at higher risk of CAD progression than those with no such family members. These risk factors are varying in different regions of the world regarding to prevalence.

Inflammation risk in Disease

It is a complex and a basic piece of immune reaction to diseases and harms to tissue. Coronary atherosclerosis is a chronic inflammatory health condition (Bernhagen et al., 2007). Inflammation processes has casual relationship with obesity and its co-morbidities DM 2 and CAD (Bastard, Maachi, Lagathu, & Kim, 2006). Inflammatory cytokines played vital role in Coronary artery disease (Goodwin, Pendleton, & Levy, 2007) obesity (Kiefer, Zeyda, Todoric, & Huber, 2008) and diabetes mellitus (Farah & Shurtz-Swirski, 2008). Inflammation pathogenesis of diseases played vital role and inflammatory markers are interleukin-6 gene (IL-6) (Satti, Hussain, & Javed, 2013), tumor narcosis factor Alpha (TNF-α) (Kolb & Mandrup-Poulsen, 2005) and Angiotensin converting enzyme (ACE) (D. Ng, Tai, Koh, Tan, & Chia, 2005) cause these diseases

Bioinformatics and System Biology

Text and literature mining is emerging as a promising area for data mining in biology (Cohen & Hersh, 2005; Jensen, Saric, & Bork, 2006). The completion of the Human Genome project, the initial elucidation of many important biological pathways, and the deluge of biological data becoming avail-able provide exciting opportunities for computer-assisted analysis of biological systems, with huge potential future impact. Text mining is also known as text data mining, which refers the process of deriving high-quality information from text. High–quality information is derived through the statistical

pattern learning (Agrawal & Batra, 2013a). It is applied to textual data. Text is unstructured, vague and difficult to deal with but it is the most common method for formal exchange of information. The goal of text mining is to derive implicit knowledge that hides in unstructured text and present it in an explicit form. This generally has four phases: document retrieval, information retrieval, information extraction with keyword matching and hypothesis generation (Agrawal & Batra, 2013a; Zhu et al., 2013).

According to literature survey it has been investigated that ACE, IL-6 and TNF-alpha genes and polymorphisms exist in different population as well as in Pakistani population causing obesity, diabetes and CAD. With the help of modern research fields like bioinformatics and system biology only inflammatory markers network analysis has been studied recently by Nair et al., 2014 in CAD. ACE and TNF-alpha network and pathway analysis in CAD had not been studied, and also these three combined genes had not been studied yet in these co-morbidity diseases.

CHAPTER 3

MATERIALS AND METHODS

To extract the information regarding mechanism of co-morbidity among CAD, obesity and diabetes, following methodology was developed. Strategy is to identify inflammatory genes involvement in each of the said disease and especially in co-morbid conditions. Latterly analysis and involvement of the inflammatory genes in diseases were carried out in pathways enrichment analysis method.

Extraction of candidate Genes involved in co morbidity

Genes related with CAD, Obesity and Diabetes mellitus were considered for the development of network. These genes were retrieved from three autonomous sources, PolySearch, GWAS database and content mining self composed java system separately.

PolySearch Tool

PolySearch (http://wishart.biology.ualberta.ca/polysearch) is a thorough content mining framework. It covers enormous biomedical ideas including diseases, genes/proteins, drugs, metabolites, SNPs, pathways and more over tissues through various biomedical content, containing databases (Cheng, Knox, Young, & Stothard, 2008).

Genome-wide association studies (GWAS)

Throughout the most recent decade, genome-wide association studies (GWAS) have turned into the standard tool for gene discovery in human disease research (Begum, Ghosh, Tseng, & Feingold, 2012).

Genome-wide association studies database or GWASdb (http://jjwanglab.org/gwasdb) gives far reaching practical annotations to each genome variant, including genomic mapping information, amino acids substitutions, evolution, gene interpretation Furthermore disease relations. Another resource which was used for collection of inflammatory genes of CAD, Obesity and DM was GWAS database (Li, Wang, Liu, Lim, & Wang, 2011).

Literature Mining

Numerous text mining techniques are applied in different fields to get desired knowledge out of huge data (Agrawal & Batra, 2013b). Content mining is an adaptable innovation that can be connected to various diverse undertakings in biology and medicine (Pletscher-Frankild, Palleja, Tsafou, & Binder, 2015). For this research task a script was written in java programming language to retrieve information based on URL and keywords related to the search topic. The Script was used to retrieve more specific research articles to the diseases and genes. Script was running online and it researched papers from desired database. It generating output file with desired papers which were manually cross checked and list of candidate gens was extracted.

Redundancy Removal

Weka is a collection of machine learning algorithms for data mining tasks. The algorithms can either be applied directly to a dataset or called from your own Java code. Weka contains tools for data pre-processing, classification, regression, clustering, association rules, and visualization. All the dataset from three resources was combined and redundancy was removed. A list of genes was finally produced Through the Weka Tool (http://www.cs.waikato.ac.nz/ml/weka/). It is platform which used for clustering, classification and preprocessing of data (Srivastava, 2014).

Explorations of Protein-Protein interaction

Protein-protein interactions (PPIs) network provide a gainful structure to a better seeing of the practical association of the proteome (Stelzl et al., 2005). PPIs are significant towards biological mechanisms. Therefore, Gathering PPI networks gives various new insights under protein functionality. Connected network according to system biology perspectives are helping to understand global association principles of functional associated cellular networks (Ge, Walhout, & Vidal, 2003). The candidate genes list was obtained from weka. STRING database version 10.5 (https://string-db.org/) was used to download protein–protein interactions after the weka list generation. It is pre-computed database to investigation, about protein–protein connections (Szklarczyk et al., 2017).

Visualization of PPIs network

Network was visualized through CytoScape software version 3.5.1. It is wonderful program, starting with analysis, operation Furthermore visualization of interactions. Cytoscape is freely available tool for biomedical interaction network visualization and construction. It can be used for integration of interacted networks with high-throughput expression data. In spite of the fact, it applicable to any interaction system, when it utilized with conjunction for extensive databases about protein-protein, protein-DNA, and hereditary collaborations it would progressively accessible to people (Shannon et al., 2003).

PPIs of selected candidate gene visualization was also validated through Pejak software (Batagelj & Mrvar, 2004). It is software used to designed for transformation of the network into smaller network and visualize them out. Some features of it are: network, vector, Partitioning, Hierarchical, permutation and clustering.

Topological analysis of protein-protein interaction network

Visualization of giant network was done through Cytoscape software version 3.5.1. The network parameters identified with network theory were handled. Properties of Nodes including availability degree (K) betweenness centrality (BC) and closeness centrality (CC) were selected to evaluate the nodes in a network; particularly k and BC were two key parameters were checked (Babur, 2010). The number of edges connected to node is called degree of node and number of shortest paths that passes through nodes is called Betweenness centrality (BC).

Extraction of hub genes network

Hub nodes are very important in biological networks. These nodes are forming backbone of whole network. Hub genes interaction is necessary to understand the backbone of network which controlling to whole network. Hence, the node with high BC and degree esteem ought to be the intensely utilized convergences; these nodes and the connections between them make up a backbone. Therefore, the nodes with high BC and K values were selected for hub. So for extraction of hub genes cutoff value for BC 0.04 and K 50 was used.

Validation of giant network and hub genes network

In order to make sure the accurateness of giant network, it was visualized from pejak tool as well. It is highly versatile tool used in Bioinformatics. BC and Degree values were also matched through it and accuracy of network was measured. For precision of our backbone network and its recurrence determination about center genes test networks were constructed through Cytoscape while using part of candidate genes which are involved in backbone network. The test networks was constructed through logic of leave on out from hub genes.

Disease-Disease Network

The network in which nodes represent the disorder and two disorders are connected to each other if they share at least one gene is called human disease network (HDN). Therefore, the same gene will be joined with two different disease pathophenotypes, this linkage may be often an evidence that those two diseases need a regular hereditary origin. Disease-disease network for the co morbidity of CAD, Obesity and Diabetes mellitus was constructed through the DisGeNET (http://www.disgenet.org) Plugin of CytoScape software. It is multipurpose software that can be utilized for various research purposes including the examination of the sub-atomic underpinnings of human disease and their co morbidities, the acceptance for computationally predicted infection genes and the assessment for text-mining techniques execution.

Disease Gene Network (DGN) for Hub Genes

A system of disorders and disease genes connected by known disorder–gene affiliations offers proposal to investigate in a single graph-theoretic framework, all identified phenotype and disease gene links, showing the normal hereditary starting point of numerous infections. Genes connected with comparative disorder demonstrate both higher probability of physical associations between their results and similarity for their transcripts expression profiles, Supporting those presence from securing unique disease-specific functional modules (Barabási, Gulbahce, & Loscalzo, 2011).

In the disease gene system nodes speak to diseased genes and two genes are associated in the event that they are related with a similar disorder. Therefore, Two genes are connected each other by node of one disorder/disease. DGN network was constructed through the DisGeNET (http://www.disgenet.org) Plugin of CytoScape software.

Molecular Functional Enrichment and Pathways Analysis

Finding functional properties of gene sets is a regular step in understanding high-throughput biological data. The establishment of enrichment investigation is that to Clustering of functionally associated factors into common set. various functional annotation databases have been produced for the classification of genes according their various similar functions in the cell the Gene Ontology (GO) is prominent amongst the most broadly utilized by numerous useful functional enrichment tool (K. Glass & Girvan, 2014). Pathway advancement investigation is a measurable approach used to find a factually critical depiction of a utilitarian pathway class inside a determination of elements from a heterogeneous factor population.

Gene set Molecular function and Pathways analysis for understanding of biological significance of hub genes was done through ClueGO (Bindea 1−4 et al., 2009). It makes easy the visualization of functionally correlated genes in clusters.

CHAPTER 4

PROPOSED CONTEXT DIAGRAM

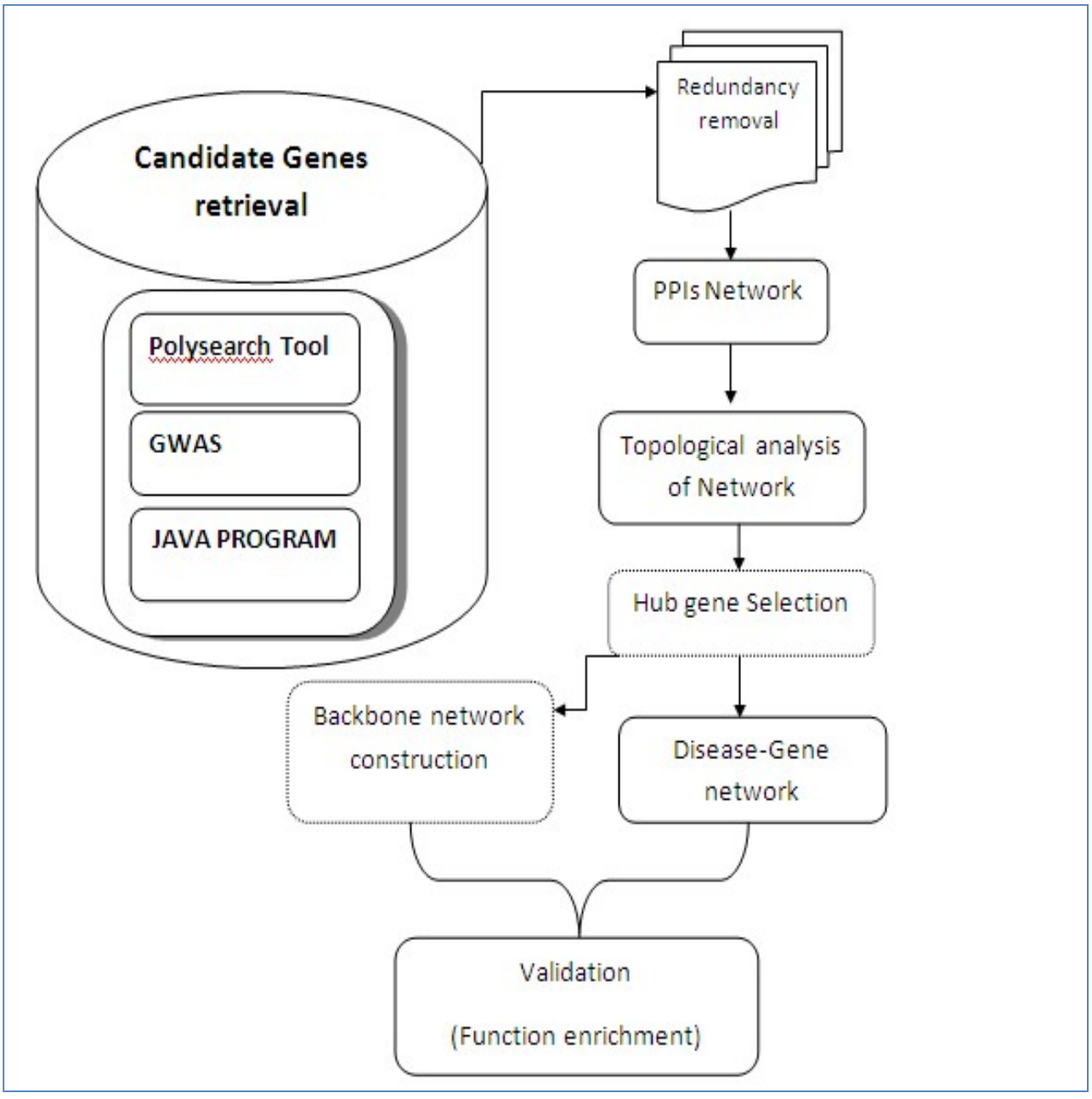

Figure 1 strategy used to identify key candidate gene in co morbidity of Obesity, Diabetes and Coronary artery disease

CHAPTER 5

RESULT AND DISCUSSION

Extraction of inflammatory Genes

Genes associated as inflammation in CAD, Obesity and Diabetes mellitus were selected for the construction of network. These genes were scrutinized from three autonomous sources, PolySearch, GWAS database and Text mining self written java program. Candidate genes related to inflammation in CAD, Obesity and Diabetes mellitus was searched by PolySearch text mining system, Which might transform an rundown from claiming ideas pertinent of the user's inquiry by examining numerous data sources including PubMed, OMIM, DrugBank What's more Swiss-Prot. The query type was selected 'Disease-Gene/Protein Association' and the query keywords were 'Coronary artery diseases', 'Obesity' and Diabetes mellitus. PolySearch system returns 1142, 169 and 175 literatures set respectively. For accuracy determination, it was manually confirmed either these genes are linked with the CAD, Obesity and Diabetes mellitus or not. Finally a total of 100, 59 and 40 candidate genes were scrutinized, which were found associated with inflammation (Annexure I). These genes were prioritized dependent upon a significance score communicated similarly as Z score, also alludes of the amount from claiming standard deviations from claiming significance score over those mean quality. A higher Z score means lesser probability that result will be because of risk. Those chose genes hosting Z score > 1 is shown in Table 1.

Table 1 Number of Candidate genes involved in co morbidity of coronary artery disease, obesity and diabetes founded by PolySearch Tool

Disease	Literature Hits	Z score >=1	Exclusion	Selected hits
CAD	1142	145	45	100
Obesity	175	45	5	40
DM	169	74	5	59
Total				199

Another resource which was used for collection of inflammatory genes of CAD, obesity and DM was GWAS database (Li et al., 2011). Genome-wide association studies database or GWASdb (http://jjwanglab.org/gwasdb) gives far reaching practical annotations to each genome variant, including genomic mapping information, amino acids substitutions, evolution, gene interpretation Furthermore disease relations. It yields 1206, 137 and 201 literature genes respectively. After duplicate removal and manual inflammatory genes validation 30, 16 and 19 genes were selected (Annexure II). Table 2 indicates the hits from GWASdb.

Table 2 Number of Candidate genes involved in co morbidity of coronary artery disease, obesity and diabetes founded by GWAS db

Disease	Literature Hits	Selected Hits
CAD	1206	30
Obesity	137	16
DM	201	19
Total		65

For Further validation of PolySearch and GWAS results a Java script was written, which took User provided different files while execution such as URL file and query keyword file. It was searching online papers from Pubmed repository and produced output file with desired papers links. These papers are manually checked and inflammatory genes were extracted. It provides a list of 70, 30 and 54 genes for CAD, Obesity and DM respectively (Annexure III). Table 3 summarized research papers and their inflammatory genes number.

Table 3 Number of Candidate genes involved in co morbidity of Coronary artery disease, Obesity and Diabetes founded by Java Program.

Disease	**No. of Links**	**Query keyword matching**	**Inflammation keywords containing paper**	**Inflammatory Genes**
CAD	144,800	20,992	230	70
Obesity	200,000	15,300	2750	30
DM	135700	19,450	712	54
Total				154

Redundancy removal

All annexure were combined with Whole dataset and redundancy was removed through Weka Tool. Redundancy removal was necessary because there was duplication of hits after combined three independent resourced datasets. Repeated values in the datasets could lead to false results; therefore for the better result accuracy it is necessary to remove duplicate values. List of candidate genes after combination and redundancy removal was shown in annexure IV.

Extraction and Visualization of PPIs network

The candidate genes list was converted to seed proteins and PPIs was downloaded from STRING database (Szklarczyk et al., 2017). STRING, 10.1 was used and Homo-sapiens organism selected for interaction. This database provides knowledge about experimental and predicted interactions from different resources like neighborhood, gene fusions etc. Network was constructed and visualize through Cytoscape v 3.5.1 software according to candidate proteins. And through network analyzer tool of Cytoscape its highly connected network extracted with 231 nodes and 2612 edges as shown in figure 2.

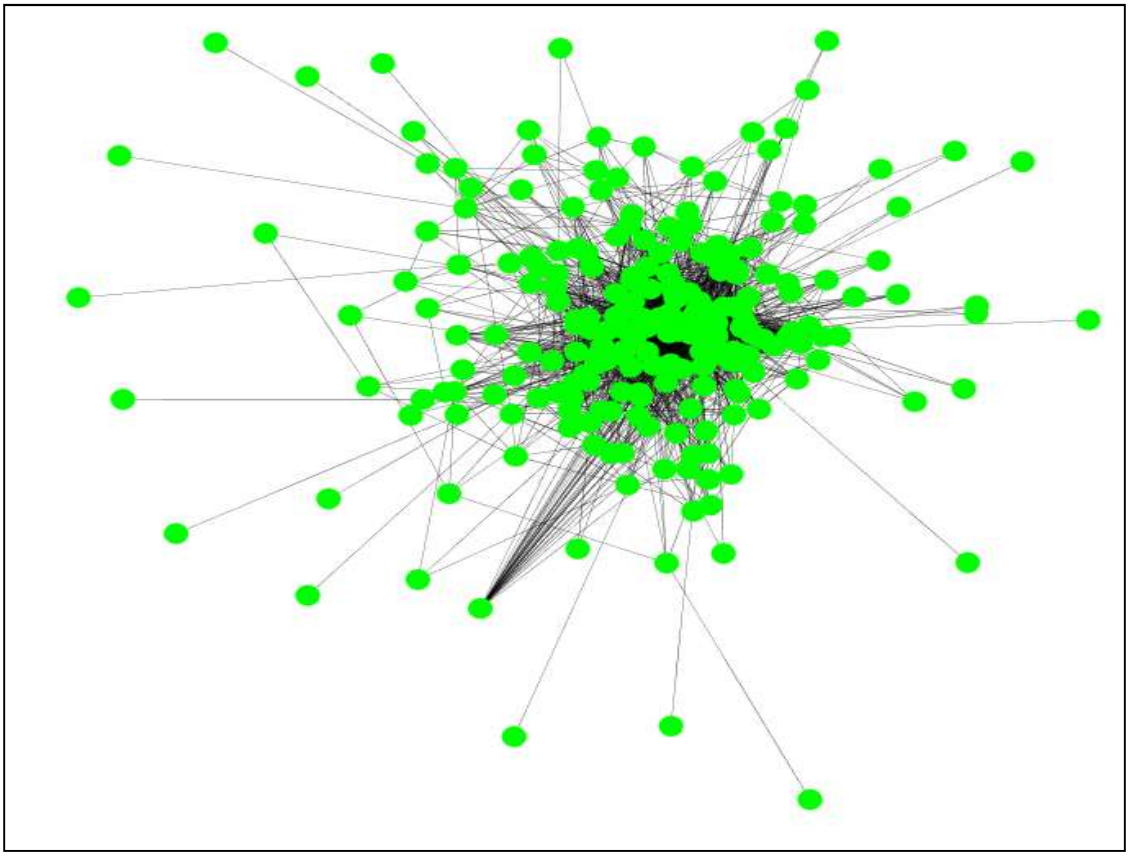

Figure 2 Giant PPIs network in Coronary artery diseases, obesity and diabetes mellitus

Topological analysis of protein-protein interaction network

Keeping in mind the end goal to dissect and handle the giant network it was visualized from Cytoscape softwer version 3.5.1. The network and its parameters were identified and handled. Properties about nodes including connectivity degree (k), betweenness centrality (BC) and closeness centrality (CC) was received to assess the hubs in a system

(Babur, 2010). Degree (k), the most essential feature for a hub in a system is characterized as the quantity of nearby connections, i.e. the quantity of communications that interface one protein to its neighbors. BC is the portion of the quantity of shortest path that go through every node, which measures how regularly nodes occur on the shortest paths between different nodes. The shortest path is ascertained by measuring the length of the considerable number of geodesics from or to the vertices in the network. A node with high BC has extraordinary impact over what streams in the system. BC may assume a noteworthy part as a global property since it is a valuable pointer for distinguishing bottlenecks in a system. Closeness centrality (CC) is characterized concerning illustration the opposite of the Normal length of the shortest paths to/from every last one of different nodes in the graph, which lets us the topological focus of the network. Total topological estimations about networks incorporate average degree and width used to character system. Normal level (<k>): it speaks to those intend of know degree values about nods in a network. Longest path distance among all shortest paths is called Diameter/width of network. In short, high degree and Betweenness centrality was used for extraction of hub genes.

Extraction of hub genes network

As reported earlier (Bastard et al., 2006; Bernhagen et al., 2007), Here also endure the involvement of inflammatory genes in development of CAD, Obesity and Diabetes. In this study, it was viewed inflammatory genes interactions maintaining the CAD, obesity and Diabetes as an important network. The genes with high BC and degree esteem strongly utilized connections in network which makes backbone of network. Backbone network is sub network which strongly stabilized global network. If node from backbone network removed than it might be break global one connected compound into several components. Therefore, 0.04 BC and > 50 degree values were used for construction of hub gene network (Nair et al., 2014). These high BC genes and the connections between them were extricated from the network to make a backbone.

This task result into 31 Top genes with High BC and K value. Annexure V was produced for hub genes and network extracted from giant network. Hub genes with high BC and K

values are shown in figure 3. Five hub genes with high degree greater than 50 and minimum Betweenness centrality of 0.04 are summarized in Table 4.

Table 4 Hub Genes involved in Coronary artery disease, Obesity and Diabetes with High Degree and BC values

Sr.No	GENE Symbol	Name	Degree	Betweenness centrality
1	INS	Insulin	141	0.167539
2	ALB	Albumin	124	0.085201
3	IL6	Interleukin- 6	111	0.05481
4	TNF	Tumor necrosis alpha	105	0.047748
5	VEGFA	Vascular endothelial growth factor A	94	0.047222

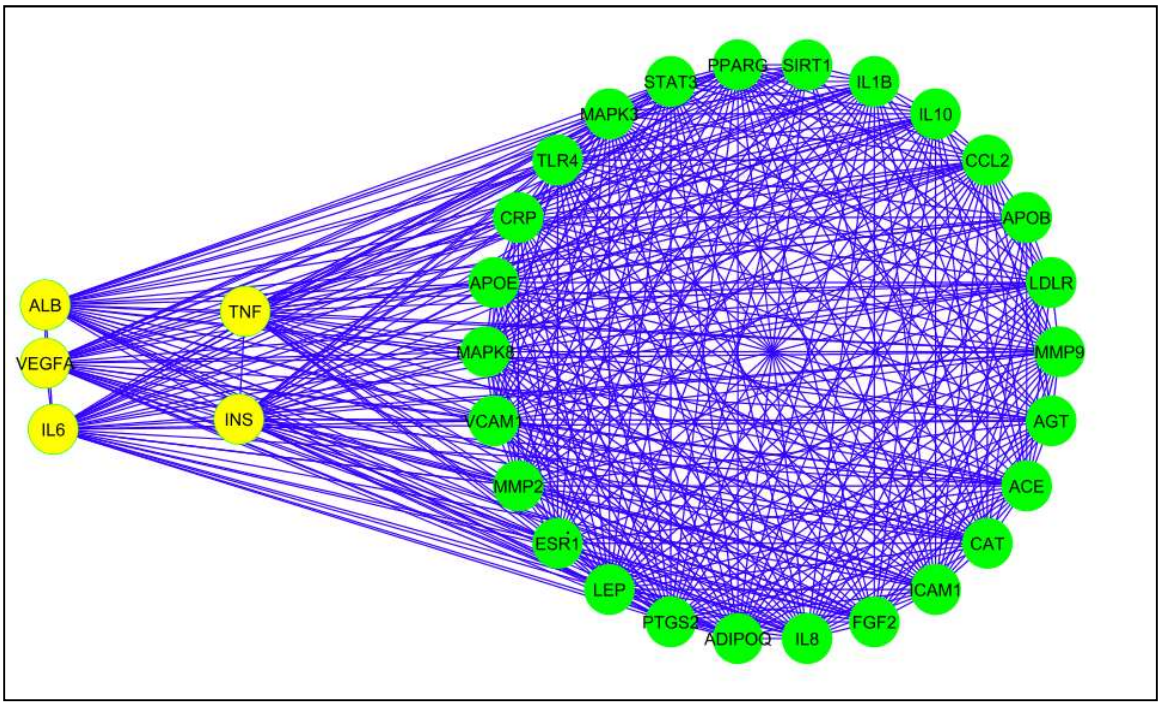

Figure 3 Hub genes network of coronary artery disease, obesity and diabetes mellitus

Validation of giant network and hub genes network

Giant network accuracy measuring and validation, it was visualized through pejak tool as well. It is highly versatile tool used in Bioinformatics. BC and Degree values were also matched through it and accuracy of network measured. Frequency measurement and estimation of constructed backbone network were evaluated by test network construction. It was done through Cytoscape while using part of candidate genes which are involved in backbone network. The test networks were constructed through logic of leave on out from hub selected 5 genes through repeated removal of top 31 nodes that had selected by 0.04 BC and > 50 Degree value. Every one node out from giant network results in construction of 31 networks. However if more than one genes were omitted it would result in larger number of combinations. Such analysis was carried out for all results in construction of total 215 (5*23+5*12+5*8) while with combination of 2, 3 and 4 genes omitting respectively. Finally 246 (215+31) networks were constructed. This analysis was performed by Cytoscape v 3.5.1. Detail list of omitted nodes is provided in annexure VI. In the end, the best 5 hubs were resolved in these 246 test networks. The precision of the network, which is the extent of the center points held in the test network to the quantity of centers (n=5) in the fundamental network, was at long last measured.

Disease- Disease Network

Human disease network for the co morbidity of CAD, obesity and diabetes was done through the DisGeNET plugin of Cytoscape. Disease Projections was selected and three independent sub-networks for three diseases were extracted from the DisGeNET. Query of coronary artery disease, obesity and diabetes results into 418, 748 and 2 nodes connected respectively. All sub-networks were merged and giant network of diseases generated and diabetes node selected. When the nearest neighbor of diabetes checked that were coronary artery disease and obesity as shown in figure 4.

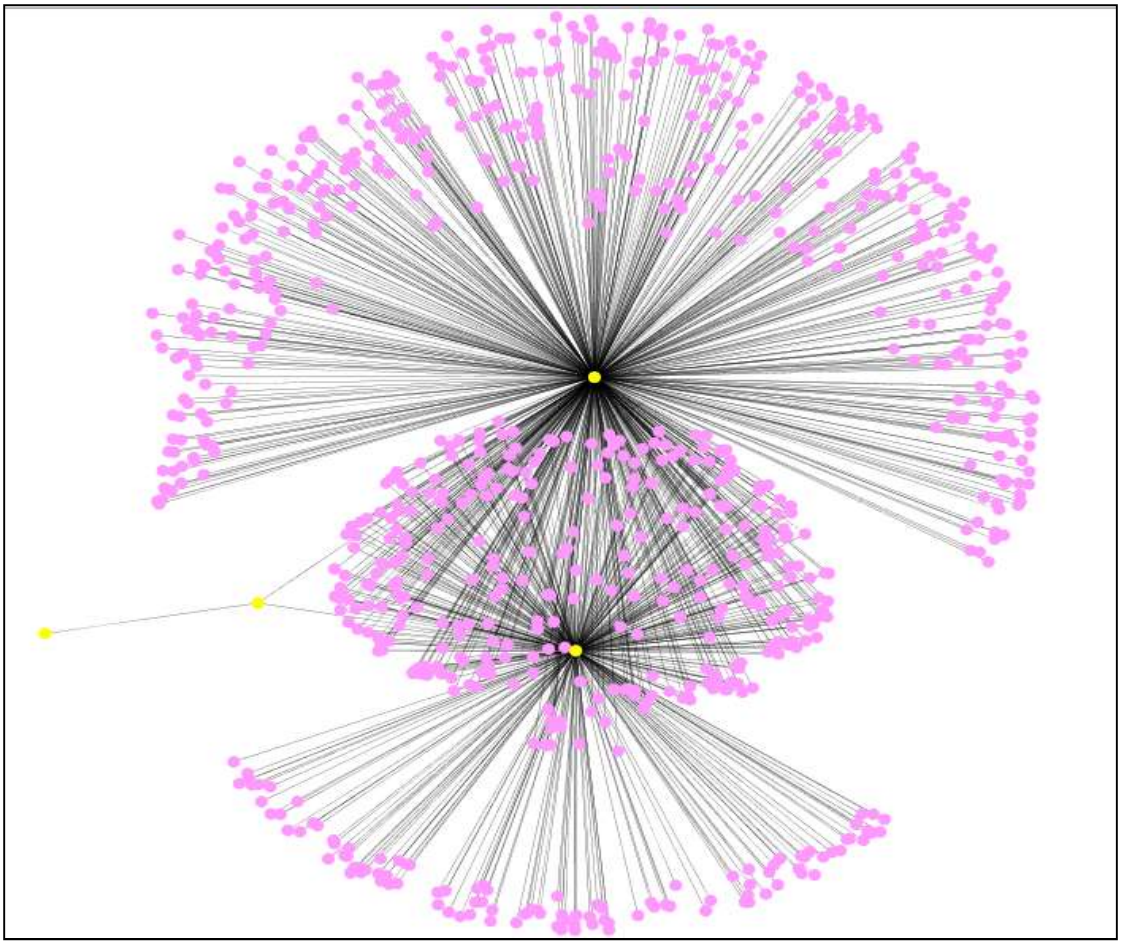

Figure 4 disease-disease network of coronary artery disease, obesity and diabetes mellitus

Disease Gene Network (DGN) for Hub Genes

In order to understand five hub genes interaction with diseases or disease interaction with hub genes, it was done by Gene-disease network construction and visualization. This network constructed through DisGeNET plugin of Cytoscape software. Five sub-networks were constructed, every time one hub gene was selected from the Disease-Gene projection module of DisGeNET application. It yields interaction of 160,102, 65, 59, 63 nodes for TNF, IL-6, VEGFA, INS and ALB respectively. Each sub network was analyzed and highly connected diseases related to gene was examined and summarized in table 5. These sub-network interactions were merged and giant Gene-disease network produced. Giant network yields into 311 nodes of interaction as shown in figure 5.

Table 5 Analysis of Hub genes association to high connectivity of disease

Gene	**Disease nodes**	**Edges**	**Connected Diseases**
TNF	160	295	Inflammation, CAD, liver , kidney
IL-6	102	149	Inflammation, cancer, heart diseases
INS	59	139	Diabetes, Obesity , metabolic disorders, hypotension
VEGFA	65	97	Myocardial ischemia, CAD, Kidney failure, Diabetes, Obesity
ALB	63	125	Cerebrovascular Accident, kidney diseases, nephritis

This table indicated relationship between hub genes and connected diseases. TNF gene is enriched in performing activities of diseases because having high degree of nodes connectivity. Other way around hub genes ALB shows least connectivity to diseases. TNF and IL-6 and are shown relation with inflammation in table.

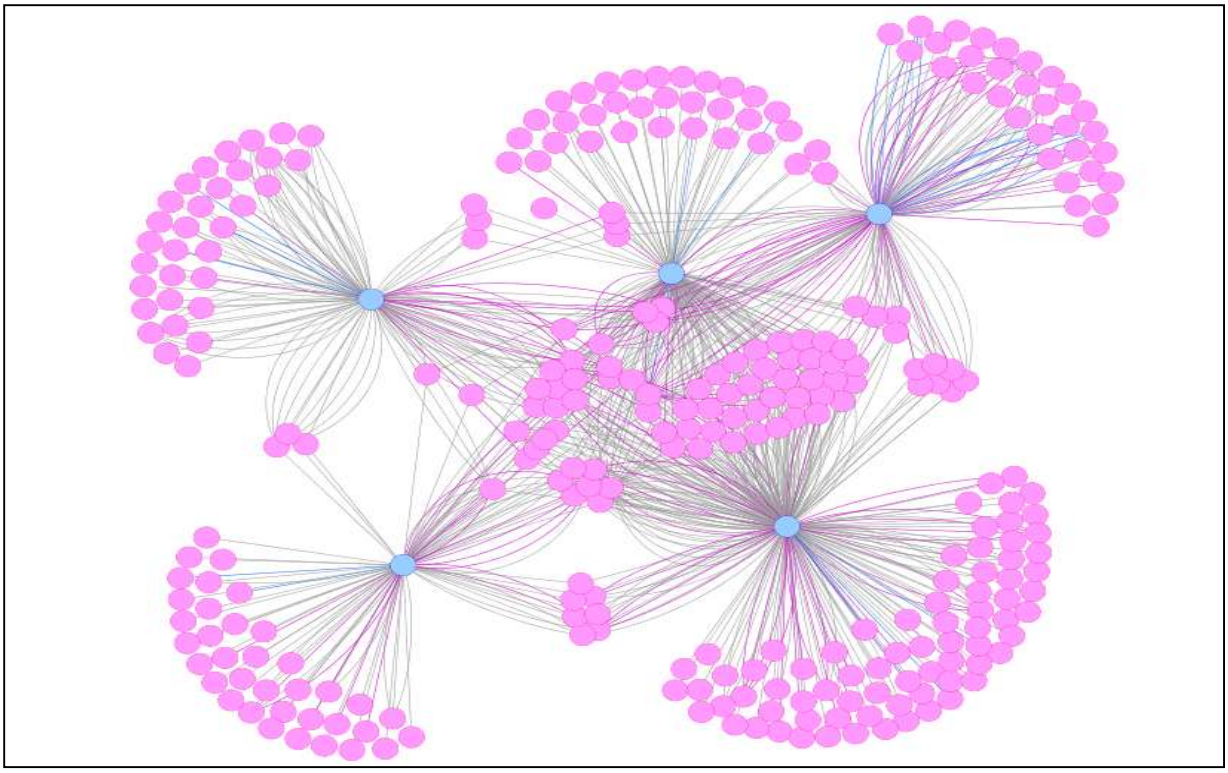

Figure 5 Coronary artery disease, Obesity and Diabetes Gene-disease interaction network

Light blue color indicates to the hub Genes, Five individual gene-disease interactions are combined to shown here in above picture. Purple color indicates diseases which are connected to genes.

For further analysis obesity, diabetes and Coronary artery disease nodes were selected from combined Gene-Disease network. It results into 18 nodes and 79 edges as shown in figure 6.

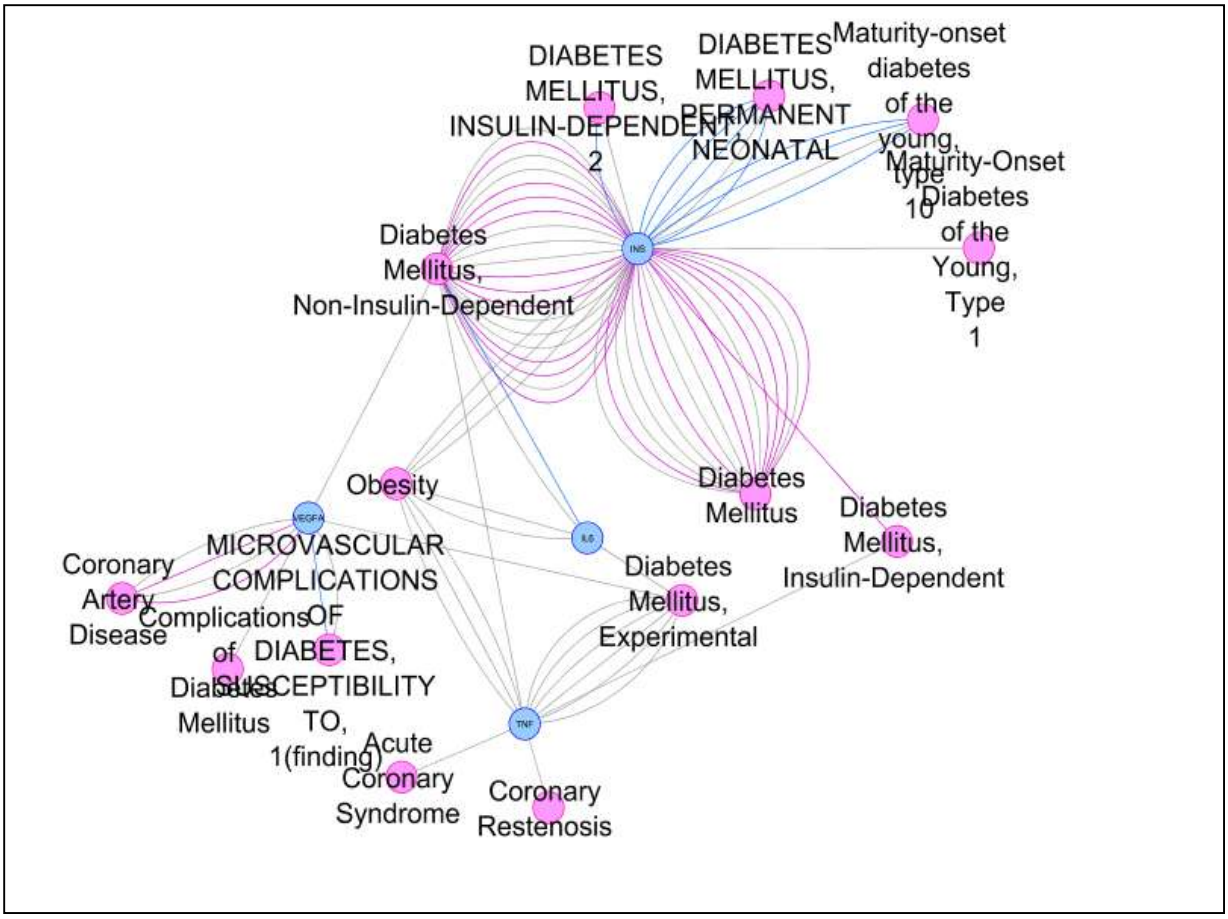

Figure 6 Coronary artery disease, Obesity and diabetes mellitus neighbor are connected through this network

This above picture shows connected relationship between hub genes and diseases of interest. One thing which comes forward that ALB gene is not connected to CAD, obesity and Diabetes Directly. Moreover, sub-sub network of Obesity, CAD and Diabetes mellitus were constructed through figure 5 network. Obesity disease sub-sub network indicated that IL6, TNF and INS gene associated with it as shown in figure 7. Diabetes disease node sub-sub network neighbor selection result into VEGFA, IL-6, INS and TNF gene association which shown in figure 8. Coronary artery disease node sub-sub network form sub-network provides result into TNF and VEGFA as shown in figure 9.

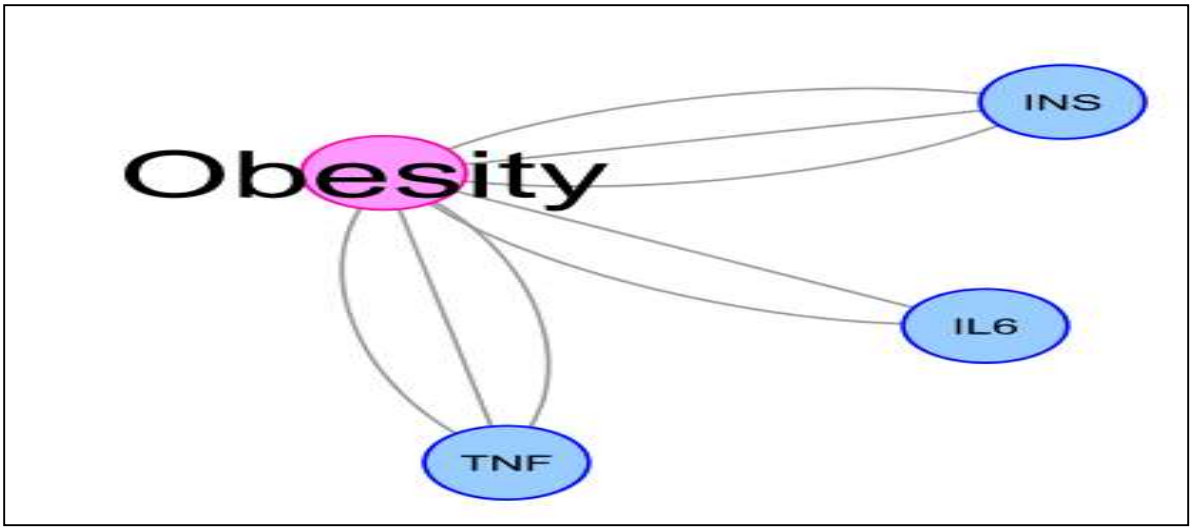

Figure 7 Obesity direct interaction showning genes

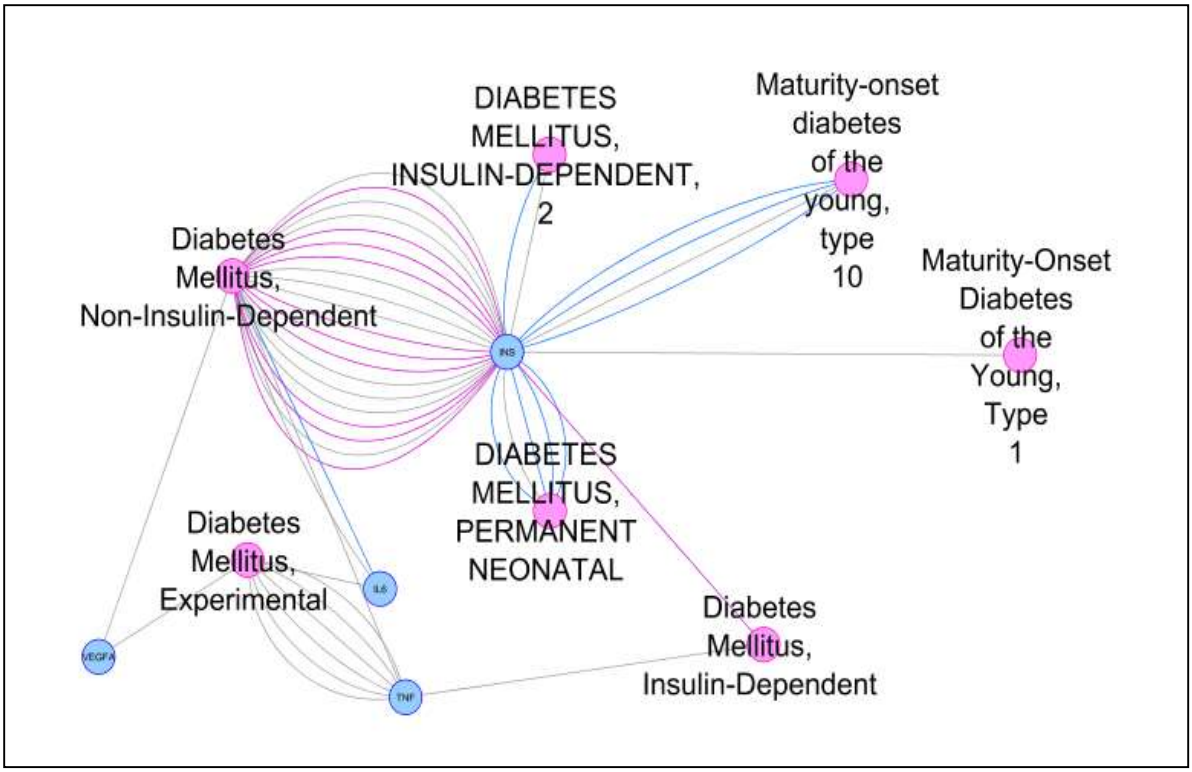

Figure 8 Diabetes Mellitus direct interaction showing Genes.

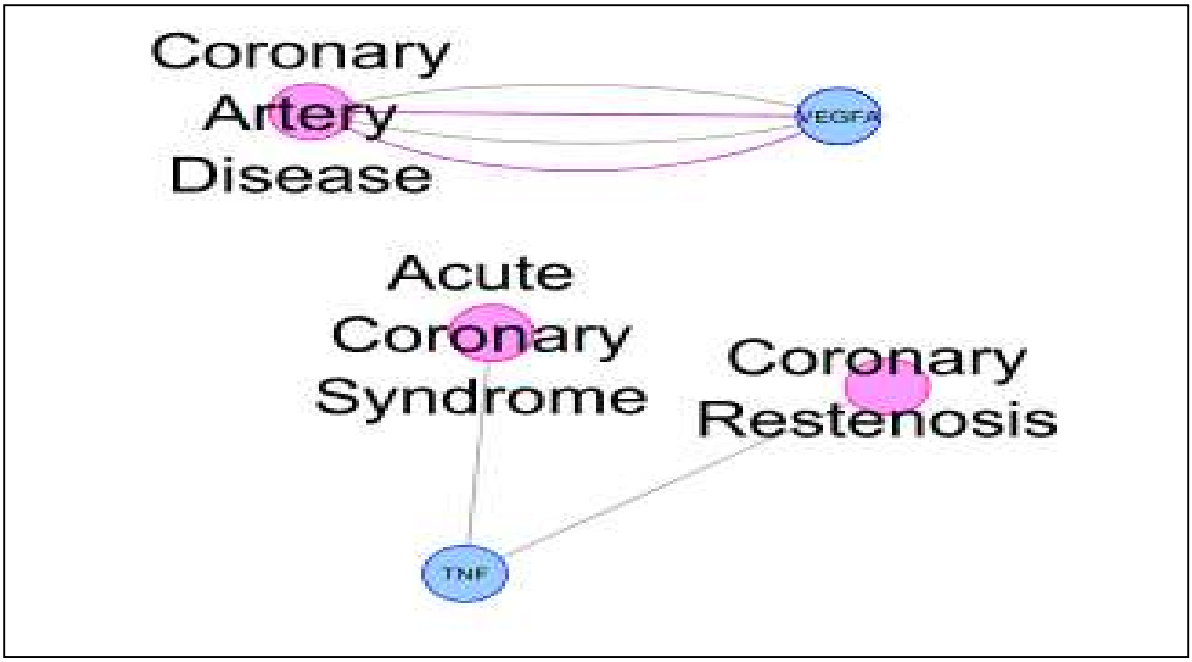

Figure 9 Coronary artery disease direct connected genes

These sub networks relationships shows different possible combination of occurance. Such as, If person suffered by obesity than the chances of having genetic problem or alteration in INS, IL-6 and TNF gene. There could be possibility that obese person could have DM and CAD if has TNF inflammation. If person suffered by diabetes mellitus, than there exist possibility of occurrence INS, TNF, IL-6, and VEGFA genetic alteration. This indicates that if person having DM and VEGFA mutation or alteration shown than person might become coronary artery disease patient or vice versa. If person having DM and TNF alteration than could be possibility of Obesity and CAD occurrence. If person suffered by Coronary artery disease than chance of obesity and DM with TNF alteration or mall functioning. DM and CAD person could share VEGFA gene. All the scenarios are summarized in Table 6.

Table 6 summarization of co morbidity genetic possibilities of Coronary artery disease, Obesity and DM

Disease	GENES	Co-morbidity
Coronary artery disease	i. TNF	Obesity, Diabetes
	ii. VEGFA	Diabetes
Obesity	i. INS or IL-6	Diabetes
	ii. TNF	CAD and Diabetes
Diabetes mellitus	i. VEGFA	CAD
	ii. TNF	Obesity ,CAD
	iii. INS or IL-6	Obesity

Molecular Functional Enrichment and Pathways Analysis

Functional properties of hub genes were analyzed and Pathways annotations enrichment was performed. Frequency of occurrences of pathways and molecular function of hub gene literately proved were analyzed through ClueGO. It makes easy the visualization of functionally correlated genes in clusters. KEGG pathways and Molecular functional annotation were performed for the set of hub genes. Kappa score was selected 0.3 which result into overall insulin resistance process and the two main signaling pathways HIF-1 and AGE-RAGE pathway in diabetic complications. Highly enrich GO terms are grouped as represented in Table 7 and figure 10.

Table 7 Grouping of network based on GO term and Pathways

GO ID	GO term	Genes	Association %	P value	Associated Genes found
KEGG 04933	AGE-RAGE Signaling pathway in diabetes complications	3	3.03	6.69E-10	IL-6,TNF, VEGFA
KEGG 04066	HIF-1 Signaling Pathway	3	3.03	6.69E-7	IL-6,INS, VEGFA
KEGG 04931	Insulin resistance	3	2.8	8.46 E-7	IL-6,INS, TNF
GO: 0048018	Receptor against activity	1	3.84	5.80E-3	VEGFA

Table 7 summarizing the result of ClueGO analysis, It includes number of gens from set of 5 hub gens associated with GO term, Percentage distribution of genes founded from total associated genes, P value and associated genes occurrence in between of specific pathway of GO term.

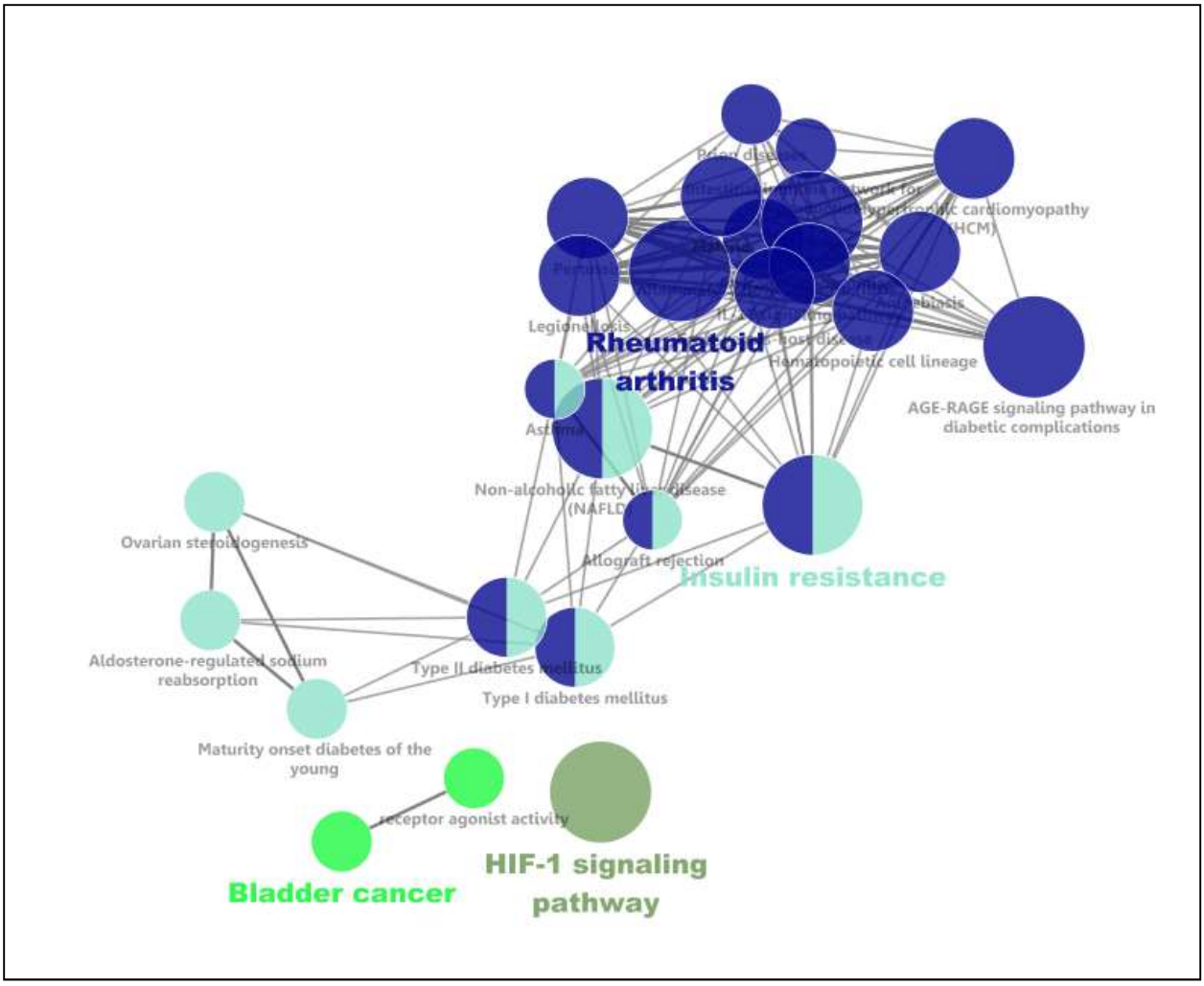

Figure 10 functionally grouped network of enriched genes association with pathways

Figure 10, representing the enriched network from GO molecular function annotation and KEGG pathways. Process of HIF-1 signaling pathway and AGE-RAGE pathway in diabetic complications were enriched by CluoGO.

More visualization is shown in below figure 11.

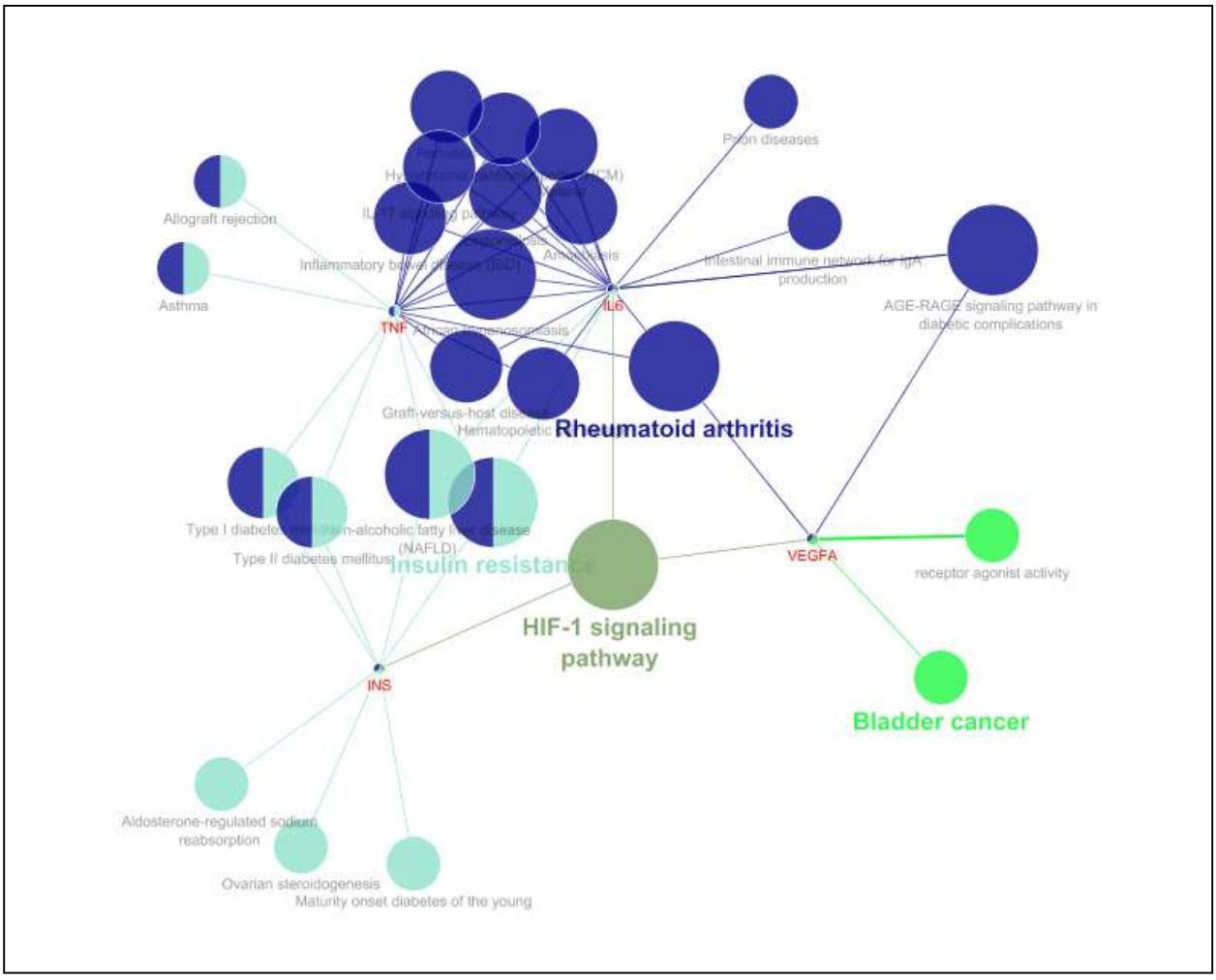

Figure 11 Gene with GO term and pathways are shown

Inflammation is significantly playing functions in Coronary artery disease (Goodwin, Pendleton, & Levy, 2007) obesity (Kiefer, Zeyda, Todoric, & Huber, 2008) and diabetes mellitus (Farah & Shurtz-Swirski, 2008) which releases various enzymes, cytokines and chemokines in development and progression of disease. Inflammatory candidate genes role has been addressed by (Nair et al., 2014) in Coronary artery disease.

Literature validation of inflammatory genes exists in co morbidity of coronary artery disease such as Obesity and Diabetes. Here in current research network based approach

used by Nair et al used in 2014, to identify key connected molecules from inflammatory genes.

Inflammatory genes are involved in various diseases but here in this research co morbidity of metabolic syndromes such as CAD, obesity and DM has been addressed. Studies on human disease-disease and disease-gene network in fact indicate a common genetic origin for many diseases. Therefore, 253 inflammation associated genes in CAD, Obesity and diabetes were used for construction, visualization and analysis of network. Analysis Results indicates 5 common hub genes such as INS, ALB, TNF, IL-6 and VEGFA in PPIs network. INS, TNF, IL6 and VEGFA were shown strong association in Obesity, diabetes and CAD in Disease-gene network. Functional Enrichment and pathways analysis shows association these diseases strong association with AGE-RAGE signaling Pathways complication in diabetics and HIF-1 signaling Pathways.

Inflammatory responses produce complex intercommunication between molecules. These responses could be autocrine or paracrine behaviors in nature. Proinflammatory responses cascades are mediated by proinflammatory cytokines or chemokine. AGE/RAGE signaling cascade demonstrated a feed-forward loop and increase RAGE expression and elevate oxidative stresses (Daffu, Pozo, & O'Shea, 2013). Elevation of circulating advanced glycation (AGEs) is believed to play a major role in the pathogenesis of DM (Ramasamy, Yan, & Schmidt, 2012).

The chief cause of morbidity and mortality in diabetes is cardiovascular disease, particularly heart attacks and strokes. Artery plaques are retrieved from human that RAGE expressed lesions and to enhanced degree in diabetes. Which shows smooth muscles and macrophages oxidative stress (Cipollone, Iezzi, Fazia, Zucchelli, & Pini, 2003).

Hypoxia inducible factor-1α (HIF-1α) is suggested to be an important upstream molecule mediating VEGF expression (Lin & Yun, 2015). In adipose tissue, hypoxia dysregulates the expression of some adipokines and proinflammatory cytokines, Such as leptin, adiponectin, IL-1, and IL-6(Wang, Wood, & Trayhurn, 2007). These cytokines are involved in down regulation of insulin signaling pathway (Jager, Grémeaux, & Cormont,

2007). IL-6 protein secretion incersesd by hypoxia these could other way around inhibits the insulin signaling pathway in adipocytes (Lin & Yun, 2015).

CHAPTER 6

CONCLUSION

Inflammation is playing critical role in co morbidity of Coronary artery disease. It is identified that IL-6, TNF, INS, VEGFA are genes playing vital role in causing inflammation of these Obesity, DM and CAD. Disease-gene Analysis helped in suggestion that TNF might be Possibility of common genetic factor for CAD disease co-morbidity. AGE/RAGE and HIF-1 Signaling pathways are linked strongly with CAD and its Co morbidity after molecular function and pathways analysis identification. ACE has not been shown as strong relationship of inflammation with disease as IL-6 and TNF, although it involved in inflammation.

CHAPTER 7

FUTURE DIRECTIONS

This research could be used for further research purpose on Precision medicine identification. It could also be used for drug target identification.

CHAPTER 8

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APPENDICES

Annexure I

List PolySearch genes

Gene ID	Gene Symbol	Abbriviation
19	ABCA1	ATP binding cassette subfamily A member 1
59272	ACE2	Angiotensin I converting enzyme 2
100	ADA	Adenosine deaminase
9370	ADIPOQ	Adiponectin
154	ADRB2	Adrenoceptor beta 2
183	AGT	Angiotensin II
213	ALB	Albumin
217	ALDH2	Mitochondrial Aldehyde dehydrogenase 2
43904	AMPKalpha	AMP-activated protein kinase alpha subunit
187	APLNR	Apelin receptor
335	APO	Apolipoprotein
335	APOA	Apolipoprotein A I
116519	APOA5	Apolipoprotein A5
338	APOB	Apolipoprotein B
345	APOC3	Apolipoprotein C3
627	BDNF	Brain derived neurotrophic factor
4879	BNP	Brain Natriuretic Peptide
775	CACNA1C	Calcium voltage-gated channel subunit alpha1 C
35070	CadN	Cadherin-N
801	CAML1	Calmodulin 1
835	CASP	Caspase activated DNase
846	CASR	Calcium sensing receptor
44048	Cat	Catalase
929	CD-14	Cycline dependant 14
947	CD34	Cycline dependant 34
948	CD36	Cycline dependent 36
925	CD8	Cycline dependent
54901	CDKAL1	CDK5 regulatory subunit associated protein 1 like 1
1029	CDKN2A	Cyclin dependent kinase inhibitor 2A
1071	CETP	Cholesteryl ester transfer protein

1236	Chemokine	C-C motif chemokine receptor 7
9575	CLOCK	Clock circadian regulator
404677	CMIT	Carotid intimal medial thickness
1401	CRP	C reactive protein
1471	CST3	Cystatin c
1490	CTGF	Connective tissue growth factor
1499	CTNNB1	Catenin beta 1
399274	CTNNB1.L	catenin beta 1 L homeolog
7139	CTNT	Troponin T, cardiac
2920	CXCL2	Chemokines
1535	CYBA	Cytochrome b-245 alpha chain
1543	CYP1A1	Cytochrome P450 family 1 subfamily A member 1
1557	CYP2C19	Cytochrome P450 family 2 subfamily C member 19
103272558	E-CDH	E cadherin
79071	ELOVL6	Elongation of long chain fatty acids
1906	END1	Endothelin 1
4850864	ERK1	Extracellular signal-regulated kinase 1
2099	ESR	Estrogen Receptor
13983	Esr2	Estrogen Receptor Beta
2167	FABP4	Fatty acid binding protein 4
2194	FASN	fatty acid synthase
7391	FCHL	Upstream transcription factor 1
547824	FERRITIN	Ferritin (protein family or complex)
197	FETUA	Fetuin A
2247	FGF2	Fibroblast growth factor 2
2629	FGF21	Fibroblast growth factor 21
8074	FGF23	Fibroblast growth factor 23
64122	FN3K	fructosamine 3 kinase
79068	FTO	Fat mass of obesity
50486	G0S2	G0/G1 switch 2
2645	GCK	Glucokinase
2646	GCKR	Glucokinase regulator
2678	GGT1	Gamma-glutamyltransferase 1
51738	GHRL	Ghrelin
2740	GLP1R	Glucagon like peptide 1
2944	GSTM1	Glutathione S-transferase mu 1
2952	GSTT1	Glutathione S transferase T1

2980	GUCA2A	Guanylin
3043	HBB	Hemoglobin
114575	HDL	High density lipoprotein
3077	HFE	Hemochromatosis
64344	HIF3A	Hypoxia inducible factor 3 alpha
3106	HLA-B	Major histocompatibility complex, class II, DR beta 1
3156	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
6927	HNF1A	Hepatocyte nuclear factor alpha [
3172	HNF4A	Hepatocyte nuclear factor 4 alpha(MODY)
100682424	HO1	Heme oxygenase 1
3240	HP	Haptoglobin
821983	HSP60	Heat shock protein 60
3306	HSP70-2	Heat shock protein family A
3383	ICAM1	Intercellular adhesion molecule 1
3479	IGF-1	Insulin like growth factor 1
111507	Igh	Immunoglobulin heavy chain complex
3600	IL 15	Interleukin15
3553	IL-1 B	IL 1 beta
3586	IL10	Interleukin 10
282863	IL-17A	Interleukin 17A
3606	IL-18	Interleukin-18
3569	IL-6	Interleukin 6
395872	IL-8	Interleukin 8
102396436	INS	Insulin
8826	IQGAP1	IQ motif containing GTPase activating protein 1
8660	IRS2	Insulin receptor substrate 2
3688	ITGB1	Integrin subunit beta 1
374209	ITGB3	Integrin subunit beta 3
3767	KCNJ11	Potassium voltage-gated channel subfamily J member 11
3931	LCAT	Lecithin-cholesterol acyltransferase
3949	LDLR	Low density lipoprotein receptor
3952	LEP	Leptin
3958	LGAL3	Galectin 3
3990	LIPC	Hepatic Lipase
41673	LKB1	Lkb1 kinase
4023	LPL	Lipoprotein Lipase
260425	MAGI3	Membrane associated guanylate kinase

4128	MAOA	Monoamine oxidase A
5607	MAP2K5	Mitogen-activated protein kinase kinase 5
4159	MC3R	Melanocortin 4 receptors
4160	MC4R	Melanocortin 4 receptors
100127112	MCP-1	Monocyte chemoattractant protein 1
4205	MEF2A	Myocyte enhancer factor 2A
4313	MMP-2	Matrix metallopeptidase 2
4314	MMP3	Matrix metallopeptidase 3
4318	MMP9	Matrix Metalloproteinase 9
4353	MPO	Myeloperoxidase
219	MTHF	Methylenetetrahydrofolate dehydrogenase
4633	MYL2	Myosin light chain 2
4684	NCAM	neural cell adhesion molecule 1
195727	Nhs	Nance-Horan syndrome
23530	NNT	Nicotinamide Nucleotide Transhydrogenase
4843	NOS2	Nitric oxide synthase 2
4846	NOSIII	Nitric Oxide 3
4878	NPPA	Natriuretic peptide A
4973	OLR1	Oxidized low density lipoprotein receptor 1
100820719	OPGB	Osteoprotegerin
64805	P2RY12	Purinergic receptor P2Y12
6596	PA	Plasminogen activator inhibitor 1
5111	PCNA	Proliferating cell nuclear antigen
5122	PCSK1	Proprotein convertase subtilisin/kexin type 1
255738	PCSK9	Proprotein convertase subtilisin/kexin type 9
5243	P-GP	P Glycoprotein
5245	PHB	Prohibitin
5322	PLA2G5	Phospholipase A2 group V
5327	PLAT	Plasminogen activator, tissue type
80339	PNPLA3	Patatin like phospholipase domain containing 3
5444	PON1	Paraoxonase 1
5465	PPARA	Peroxisome proliferator activated receptor alpha
5468	PPARG	Peroxisome proliferator activated receptors
5468	PPARgamma	Peroxisome proliferator activated receptor gamma
100861193	PROLACTIN	PROLACTIN protein
354	PSA	Prostate specific antigen
5806	PTX3	Pentraxin 3

177	RAGE	Advanced glycosylation end-product specific receptor
56729	RETN	Resistin
6198	RPS6KB1	Ribosomal protein S6 kinase B1
6402	SELL	Selectin L
23411	SIRT1	Sirtuin 1
6532	SLC6A4	Solute carrier family 6 member 4
100308165	SMA	Semispinalis lean area
6720	SREBF1	sterol regulatory element binding transcription factor 1
6774	STAT3	Signal transducer and activator of transcription 3
6934	TCF7L2	Transcription factor 7 like 2
7056	THBD	Thrombomodulin
2147	Thrombin	Thrombin
7099	TLR4	Toll like receptor 8
7124	TNF	Tumor necrosis factor alpha
7137	TNNI3	Cardiac Troponin I
7139	TNNT2	Troponin T2, cardiac type
7173	TPO	Thyroid peroxidase
193034	TRPV1	Transient receptor potential cation channel
10911	UTS2	Urotensin II
7412	VCAM1	Vascular cell adhesion molecule 1
22340	VEGF	Vascular endothelial growth factor
7422	VEGFA	Vascular endothelial growth factor A
10135	VF	Visfatin
7431	VIM	Vimentin
619537	VV	Varicose veins
7450	VWF	Von Willebrand factor

Annexure II

List of GENES from GWASdb

GENE ID	Obesity Genesymbol	Abbriviation
627	BDNF	Brain derived neurotrophic factor
7021	TFAP2B	Transcription factor AP-2 beta
2696	GIPR	Gastric inhibitory polypeptide receptor
5607	MAP2K5	Mitogen-activated protein kinase kinase 5
51086	TNNI3K	TNNI3 interacting kinase
79874	RABEP2	Rabaptin, RAB GTPase binding effector protein 2
57521	RPTOR	Regulatory associated protein of MTOR complex 1
4685	NCAM2	Neural cell adhesion molecule 2
5101	PCDH9	Protocadherin 9
51741	WWOX	WW domain containing oxidoreductase
80216	ALPK1	Alpha kinase 1
375449	MAST4	Microtubule associated serine/threonine kinase family member 4
56288	PARD3	Par-3 family cell polarity regulator
2475	MTOR	Mechanistic target of rapamycin
29969	MDFIC	MyoD family inhibitor domain containing
79068	FTO	Fat mass of obesity
158219	TTC39B	Tetratricopeptide repeat domain 39B
22926	ATF6	Activating transcription factor 6
50807	ASAP1	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1
965	CD58	Cycline Dependant Kinase
4978	OPCML	Opioid binding protein/cell adhesion molecule like
238	ALK	ALK receptor tyrosine kinase
4919	ROR1	Receptor tyrosine kinase like orphan receptor 1
4126	MANBA	Mannosidase beta
6196	RPS6KA2	Ribosomal protein S6 kinase A2
102	ADAM10	ADAM metallopeptidase domain 10
54828	BCAS3	BCAS3, microtubule associated cell migration factor
1579	CYP4A11	Cytochrome P450 family 4 subfamily A member 11
23194	FBXL7	F-box and leucine rich repeat protein 7
53841	CDHR5	Cadherin related family member 5
26034	IPCEF1	Interaction protein for cytohesin exchange factors 1
11122	PTPRT	Protein tyrosine phosphatase, receptor type T
54970	TTC12	Tetratricopeptide repeat domain 12

729582	DIRC3	Disrupted in renal carcinoma 3
1630	DCC	DCC netrin 1 receptor
64241	ABCG8	ATP binding cassette subfamily G member 8
1030	CDKN2B	Cyclin-dependent kinase inhibitor B
1030	CDKN2B-AS1	CDKN2B antisense RNA 1
54805	CNNM2	Cyclin and CBS domain divalent metal cation transport mediator 2
1282	COL4A1	Collagen type IV alpha 1 chain
1284	COL4A2	Collagen type IV alpha 2 chain
1909	EDNRA	Endothelin receptor type A
2242	FES	Feline sarcoma oncogene
2321	FLT1	Fms related tyrosine kinase 1
5045	FURIN	Furin, paired basic amino acid cleaving enzyme
2982	GUCY1A3	Guanylate cyclase 1 soluble subunit alpha
9734	HDAC9	Histone deacetylase 9
84439	HHIPL1	Hedgehog interacting protein-like 1
	IL6R	Interleukin 6 receptor
8645	KCNK5	Potassium two pore domain channel subfamily K member 5
25802	LMOD1	Leiomodin 1
4018	LPA	Lipoprotein(a)
80350	LPAL2	Lipoprotein(a) like 2, pseudogene
4023	LPL	Lipoprotein lipase
375056	MIA3	Melanoma inhibitory activity
22808	MRAS	Muscle RAS oncogene homolog
25902	MTHFD1L	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like
5175	PECAM1	Platelet and endothelial cell adhesion molecule 1
221692	PHACTR1	Phosphatase and actin regulator 1
8613	PPAP2B	Phosphatidic acid phosphatase type 2B
10544	PROCR	Protein C receptor
6583	SLC22A4	Solute carrier family 22 member 4
6621	SNAPC4	Small nuclear RNA activating complex polypeptide 4
6943	TCF21	Transcription factor 21
81615	TMEM163	Transmembrane protein 163

Annexure III

List of Java Script mined genes

PMID	GENE	Abbriviation
1.7E+07	APOE	Apolipoprotein E
1.7E+07	TRLs	Triglyceride rich lipoproteins
8357335	ACE	Angiotensin converting enzyme
2.5E+07	ABCA1	ATP-binding cassette transporter A1
1.9E+07	ACP1	Acid phosphatase locus 1
1.9E+07	TAFI	Thrombin activatable fibrinolysis inhibitor
2.5E+07	NF-κB	Nuclear factor-κB
2.5E+07	mTOR	Mammalian target of rapamycin
1.6E+07	KLOTHO	Aging syndrom gene
2.7E+07	AGTR1	Angiotensin II type-1 receptor
1.9E+07	FABP2	Fatty acid-binding protein
1.7E+07	CASR	Calcium-sensing receptor
2.7E+07	ALDH2	Aldehyde dehydrogenase 2
2.3E+07	VDR	Vitamin D receptor
2.7E+07	APJ	Angiotensin receptor-like 1
2.3E+07	FGB	Fibrinogen β
2.3E+07	CETP	Cholesteryl ester transfer protein
2.2E+07	APOA1	Apo lipoprotein A1
2.3E+07	ALOX5	5-lipoxygenase
2.3E+07	SDF-1 alpha	Stromal-derived factor-1 alpha
2E+07	TGFss	Transforming growth factor ss
2.8E+07	FADS	Fatty acid desaturase
2.4E+07	RANTES	Regulated on activation normal T cell expressed and secreted
2.6E+07	MLL5	Histone-lysine N-methyltransferase
2.8E+07	HNF1A	Hepatocyte nuclear factor-1α
1.8E+07	CYP1A1	Cytochrome P4501A1
2.3E+07	RETN	Resistin
2.2E+07	TSP- 1	Thrombospondin-1
2.5E+07	TREM-1	Triggering Receptor Expressed on Myeloid Cells-
2.7E+07	VWF	Von Willebrand factor
1E+07	GP	Glycoprotein IIIa
2.4E+07	PON	Paraoxonase
2.2E+07	OLR1	Oxidized-lipoprotein receptor 1
2E+07	ALOX5AP	5-lipoxygenase activating protein

1.7E+07	beta3-AR	Beta3-adrenoceptor
1.8E+07	CRP	C-reactive protein
2.3E+07	PPARγ	Peroxisome Proliferator-activated Receptor Gamma gene
2.5E+07	IL-21	Interleukin-21
2.5E+07	HO-1	Heme oxygenase 1 gene
2.5E+07	ADA	Adenosine deaminase
2.5E+07	anti-oxLDL	Antioxidized low-density lipoprotein
2.5E+07	MMP-9	Matrix metalloproteinase-9
2.5E+07	Lp-PLA2	Lipoprotein-associated Phospholipase A2
2.5E+07	apoM	proximal promoter region of apolipoprotein M
2.5E+07	ACAT-1	acyl-CoA:cholesterol acyltransferase-1
2.5E+07	IL-24	interleukin-24
2.5E+07	IL-1	pro-inflammatory interleukin
2.5E+07	COX-2	Cyclooxygenase-2
1.6E+07	LPL	Lipoprotein Lipase
2.4E+07	ADIPOQ	Adiponectin Q
2E+07	TNF-alpha	Tumor Necrosis Factor-Alpha
1.5E+07	CYP11B2	Adosterone synthase
1.8E+07	RAGE	Receptor for Advanced glycation end products
2E+07	VEGF	Vascular endothelial growth factor
9484992	fibrinogen beta	fibrinogen beta
1.5E+07	PAI-1	Plasminogen activator inhibitor-1
2.6E+07	MTHFR	Methylenetetrahydrofolate reductase
1.8E+07	APOB	Apolipoprotein B
2.3E+07	HL	Hepatic lipase
1.6E+07	CRP	C-reactive protein
1.8E+07	NO	nitric oxide synthase
2.4E+07	CYBA	Cytochrome b245 alpha
2.5E+07	NFKB1	Nuclear factor kappa-light-chain enhancer of activated B cells
2.6E+07	TEAD	Transcription factor binding site
2.1E+07	IF-Y	Interferon-γ
1.6E+07	AT1R	Angiotensin II type-1 receptor
2.2E+07	HDL	High-density lipoproteins cholesterol
3907293	LDL	Low density lipoprotein
1.5E+07	FVL	Factor V Leiden mutation
2.2E+07	KL	Klotho
2.8E+07	FTO	Fat mass and obesity-associated gene
2.8E+07	GR	Glucocorticoid receptor

2.8E+07	*MC4R*	Melanocortin-4 receptor
2.8E+07	*BDNF*	Brain-derived neurotrophic factor
2.8E+07	RETN	Resistin
2.8E+07	MC3R	Melanocortin 3 receptor
2.8E+07	IL-ß	Interleukin-1ß
2.8E+07	IL-8	Interleukin-8
2.8E+07	ADIPOR2	Adiponectin receptor 2
2.8E+07	SREBF1	Sterol Regulatory Element Binding Protein 1 Gene
2.8E+07	IL-10	Interleukin (IL)-10
2.8E+07	PPARγ	peroxisome proliferator-activated receptor γ
2.8E+07	IRF3	Interferon regulatory factor 3
2.8E+07	GLP-1	Glucagon-like peptide
2.8E+07	sDPP4	Dipeptidyl peptidase 4
2.8E+07	PLIN	Perilipin gene
2.8E+07	WNT4	wingless-type MMTV integration site family, member 4
2.8E+07	WNT5A	Wnt family member 5A
2.8E+07	HMOX1	heme oxygenase 1
2.8E+07	IL-17	interleukin-17A
2.8E+07	FXR	farnesoid X-activated receptor
2.8E+07	TNF)-α	tumor necrosis factor
2.8E+07	ADIPOQ	Adiponectin
2.8E+07	LEP	leptin
2.7E+07	GLP-1	glucagon-like peptide-1
2.7E+07	VEGFB	vascular endothelial growth factor B
28270386	CRP	C-reactive protein
28223291	CTRP7	C1q/TNF-related protein 7
	TLR4,	
	GLUT4	
2.8E+07	IL-1β	Interleukin
2.8E+07	IL-6	Interleukin -6
2.8E+07	TNF-α	Tumor necrosis factor-Alpha
2.8E+07	NOS	Nitric oxide synthase
2.8E+07	HMGB 1	High mobility group box 1
2.8E+07	PAI-1	Plasminogen activator inhibitor type 1
2.8E+07	Chemotactant protein-1	MCP-1
2.8E+07	CRP	C-reactive protein
2.7E+07	Angiopoietin-1	Ang1
2.7E+07	Angiopoietin-2	Ang2

2.8E+07	TLR4	Toll-like receptor 4
2.8E+07	NF-κB	Nuclear factor kappa B
2.7E+07	VEGFA	Vascular endothelial growth factor A
2.7E+07	PGE2	Prostaglandin E2
2.7E+07	IFN-γ	Interferon
2.7E+07	TXNIP	Thioredoxin-interacting protein
2.7E+07	VAP-1	Vascular adhesion protein-1
2.7E+07	DPP4	Dipeptidyl peptidase-4
2.7E+07	FKN	Fractalkine
26475041	PPARγ	Peroxisome proliferator-activated receptor-γ
2.6E+07	IL-17	Interleukin -17
2.6E+07	LDL-C	low-density lipoprotein cholesterol
2.8E+07	IL-8	Interlukine-8
2.8E+07	IL-18	Interleukin -18
2.8E+07	TRAF6	tumor necrosis factor receptor-associated factor 6
2.7E+07	VEGF	vascular endothelial growth factors
2.6E+07	ACEi	Angiotensin converting enzyme inhibitors (ACEi
2.5E+07	IL-23	Interleukin-23
2.5E+07	BDNF	brain-derived neurotrophic factor
2.5E+07	Angptl8	Angiopoietin-like protein 8
2.5E+07	ADIPOQ	Adiponectin
2.5E+07	NLRP	NOD-like receptor
2.5E+07	MMP2	Matrix metalloproteinases 2
2.5E+07	MMP9	Matrix metalloproteinases 9
2.5E+07	ICAM-1	Intercellular cell adhesion molecule-1
2.5E+07	IGF-1	Insulin-like growth factor 1
24846859	PDGF	Platelet-derived growth factor
2.5E+07	TCF7L2	
2.5E+07	JNK	C-Jun N-terminal kinase
2.5E+07	IL-34	Interleukin -34
24675103	FKN	Fractalkine
24367624	PEDF	Pigment epithelium-derived factor
2.7E+07	PGE2	Prostaglandin E2
2.7E+07	CTLA-4	Cytotoxic T lymphocyte antigen-4
2.8E+07	LDLR	Low-density lipoprotein receptor
2.8E+07	VEGF	Vascular endothelial growth factor
2.8E+07	HDL	High-density lipoprotein
2.8E+07	TG	Triglyceride

2.7E+07	NFE2L2	Nuclear factor erythroid 2-like 2
2.8E+07	NOS	Nitric oxide synthase
2.8E+07	MASP-1	Mannan-binding associated serine proteases
2.8E+07	MTHFR	
2.4E+07	PGS2/COX2	Prostaglandin synthase 2/cyclooxygenase 2
8907298	Fibrinogen	Fibrinogen

Annexure IV

List of inflammation causing genes

Sr.No	Gene ID	Symbol	Description
1	19	ABCA1	ATP binding cassette subfamily A member 1
2	64241	ABCG8	ATP binding cassette subfamily G member 8
3	38	ACAT-1	Acyl-CoA:cholesterol acyltransferase-1
4	1636	ACE	Angiotensin converting enzyme
5	59272	ACE2	Angiotensin I converting enzyme 2
6	52	ACP1	Acid phosphatase locus 1
7	100	ADA	Adenosine deaminase
8	102	ADAM10	ADAM metallopeptidase domain 10
9	9370	ADIPOQ	Adiponectin
10	154	ADRB2	Adrenoceptor beta 2
11	183	AGT	Angiotensin II
12	213	ALB	Albumin
13	217	ALDH2	Mitochondrial Aldehyde dehydrogenase 2
14	240	ALOX5	5-lipoxygenase
15	80216	ALPK1	Alpha kinase 1
16	43904	AMPKalpha	AMP-activated protein kinase alpha subunit
17	55908	ANGPTL8	Angiopoietin-like protein 8
18	187	APJ	Angiotensin receptor-like 1

19	187	APLNR	Apelin receptor
20	335	APO	Apolipoprotein
21	335	APOA	Apolipoprotein A I
22	116519	APOA5	Apolipoprotein A5
23	338	APOB	Apolipoprotein B
24	345	APOC3	Apolipoprotein C3
25	348	APOE	Apolipoprotein E
26	55937	APOM	proximal promoter region of apolipoprotein M
27	50807	ASAP1	ArfGAP with SH3 domain, ankyrin repeat and PH domain 1
28	22926	ATF6	Activating transcription factor 6
29	54828	BCAS3	BCAS3, microtubule associated cell migration factor
30	627	BDNF	Brain derived neurotrophic factor
31	4879	BNP	Brain Natriuretic Peptide
32	775	CACNA1C	Calcium voltage-gated channel subunit alpha1 C
33	35070	CadN	Cadherin-N
34	801	CAML1	Calmodulin 1
35	835	CASP	Caspase activated DNase
36	44048	Cat	Catalase
37	929	CD-14	Cycline dependant 14
38	947	CD34	Cycline dependant 34
39	948	CD36	Cycline dependent 36
40	965	CD58	Cycline Dependant Kinase
41	925	CD8	Cycline dependent
42	53841	CDHR5	Cadherin related family member 5
43	54901	CDKAL1	CDK5 regulatory subunit associated protein 1 like 1
44	1029	CDKN2A	Cyclin dependent kinase inhibitor 2A
45	1030	CDKN2B	Cyclin-dependent kinase inhibitor B

46	1030	CDKN2B-AS1	CDKN2B antisense RNA 1
47	1071	CETP	Cholesteryl ester transfer protein
48	1236	Chemokine	C-C motif chemokine receptor 7
49	9575	CLOCK	Clock circadian regulator
50	404677	CMIT	Carotid intimal medial thickness
51	54805	CNNM2	Cyclin and CBS domain divalent metal cation transport mediator 2
52	1282	COL4A1	Collagen type IV alpha 1 chain
53	6775079	COX-2	Cyclooxygenase-2
54	1401	CRP	C reactive protein
55	1471	CST3	Cystatin c
56	1490	CTGF	Connective tissue growth factor
57	1493	CTLA-4	Cytotoxic T lymphocyte antigen-4
58	1499	CTNNB1	Catenin beta 1
59	399274	CTNNB1.L	catenin beta 1 L homeolog
60	7139	CTNT	Troponin T, cardiac
61	2920	CXCL2	Chemokines
62	1535	CYBA	Cytochrome b-245 alpha chain
63	1585	CYP11B2	Adosterone synthase
64	1543	CYP1A1	Cytochrome P450 family 1 subfamily A member 1
65	1557	CYP2C19	Cytochrome P450 family 2 subfamily C member 19
66	1630	DCC	DCC netrin 1 receptor
67	729582	DIRC3	Disrupted in renal carcinoma 3
68	1803	DPP4	Dipeptidyl peptidase-4
69	103272558	E-CDH	E cadherin
70	1909	EDNRA	Endothelin receptor type A
71	79071	ELOVL6	Elongation of long chain fatty acids
72	1906	END1	Endothelin 1

73	4850864	ERK1	Extracellular signal-regulated kinase 1
74	2099	ESR	Estrogen Receptor
75	13983	Esr2	Estrogen Receptor Beta
76	2169	FABP2	Fatty acid-binding protein
77	2167	FABP4	Fatty acid binding protein 4
78	3992	FADS	Fatty acid desaturase
79	2194	FASN	fatty acid synthase
80	23194	FBXL7	F-box and leucine rich repeat protein 7
81	7391	FCHL	Upstream transcription factor 1
82	547824	FERRITIN	Ferritin (protein family or complex)
83	2242	FES	Feline sarcoma oncogene
84	197	FETUA	Fetuin A
85	2244	FGB	Fibrinogen β
86	2247	FGF2	Fibroblast growth factor 2
87	2629	FGF21	Fibroblast growth factor 21
88	8074	FGF23	Fibroblast growth factor 23
89	2321	FLT1	Fms related tyrosine kinase 1
90	64122	FN3K	fructosamine 3 kinase
91	79068	FTO	Fat mass of obesity
92	5045	FURIN	Furin, paired basic amino acid cleaving enzyme
93	50486	G0S2	G0/G1 switch 2
94	2645	GCK	Glucokinase
95	2646	GCKR	Glucokinase regulator
96	2678	GGT1	Gamma-glutamyltransferase 1
97	51738	GHRL	Ghrelin
98	2696	GIPR	Gastric inhibitory polypeptide receptor
99	2740	GLP1R	Glucagon like peptide 1

100	2944	GSTM1	Glutathione S-transferase mu 1
101	2952	GSTT1	Glutathione S transferase T1
102	2980	GUCA2A	Guanylin
103	2982	GUCY1A3	Guanylate cyclase 1 soluble subunit alpha
104	3043	HBB	Hemoglobin
105	9734	HDAC9	Histone deacetylase 9
106	114575	HDL	High density lipoprotein
107	3077	HFE	Hemochromatosis
108	64344	HIF3A	Hypoxia inducible factor 3 alpha
109	3990	HL	Hepatic lipase
110	3106	HLA-B	Major histocompatibility complex, class II, DR beta 1
111	3156	HMGCR	3-hydroxy-3-methylglutaryl-CoA reductase
112	6927	HNF1A	Hepatocyte nuclear factor alpha [
113	3172	HNF4A	Hepatocyte nuclear factor 4 alpha(MODY)
114	100682424	HO1	Heme oxygenase 1
115	3240	HP	Haptoglobin
116	821983	HSP60	Heat shock protein 60
117	3306	HSP70-2	Heat shock protein family A
118	3383	ICAM1	Intercellular adhesion molecule 1
119	3479	IGF-1	Insulin like growth factor 1
120	111507	Igh	Immunoglobulin heavy chain complex
121	3600	IL 15	Interleukin15
122	3553	IL-1 B	IL 1 beta
123	3586	IL10	Interleukin 10
124	282863	IL-17A	Interleukin 17A
125	3606	IL-18	Interleukin-18
126	59067	IL-21	Interleukin-21

127	51561	IL-23	Interleukin-23
128	11009	IL-24	interleukin-24
129	146433	IL-34	Interleukin -34
130	3569	IL-6	Interleukin 6
131	395872	IL-8	Interleukin 8
132	102396436	INS	Insulin
133	26034	IPCEF1	Interaction protein for cytohesin exchange factors 1
134	8826	IQGAP1	IQ motif containing GTPase activating protein 1
135	3661	IRF3	Interferon regulatory factor 3
136	8660	IRS2	Insulin receptor substrate 2
137	3688	ITGB1	Integrin subunit beta 1
138	374209	ITGB3	Integrin subunit beta 3
139	3767	KCNJ11	Potassium voltage-gated channel subfamily J member 11
140	8645	KCNK5	Potassium two pore domain channel subfamily K member 5
141	9365	KL	Klotho
142	3931	LCAT	Lecithin-cholesterol acyltransferase
143	3949	LDLR	Low density lipoprotein receptor
144	3952	LEP	Leptin
145	3958	LGAL3	Galectin 3
146	3990	LIPC	Hepatic Lipase
147	41673	LKB1	Lkb1 kinase
148	25802	LMOD1	Leiomodin 1
149	4018	LPA	Lipoprotein(a)
150	4023	LPL	Lipoprotein Lipase
151	260425	MAGI3	Membrane associated guanylate kinase
152	4126	MANBA	Mannosidase beta
153	4128	MAOA	Monoamine oxidase A

154	5648	MASP-1	Mannan-binding associated serine proteases
155	375449	MAST4	Microtubule associated serine/threonine kinase family member 4
156	4159	MC3R	Melanocortin 4 receptors
157	4160	MC4R	Melanocortin 4 receptors
158	100127112	MCP-1	Monocyte chemoattractant protein 1
159	29969	MDFIC	MyoD family inhibitor domain containing
160	4205	MEF2A	Myocyte enhancer factor 2A
161	375056	MIA3	Melanoma inhibitory activity
162	4313	MMP-2	Matrix metallopeptidase 2
163	4314	MMP3	Matrix metallopeptidase 3
164	4318	MMP9	Matrix Metalloproteinase 9
165	4353	MPO	Myeloperoxidase
166	22808	MRAS	Muscle RAS oncogene homolog
167	219	MTHF	Methylenetetrahydrofolate dehydrogenase
168	25902	MTHFD1L	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like
169	2475	MTOR	Mechanistic target of rapamycin
170	4633	MYL2	Myosin light chain 2
171	4684	NCAM	neural cell adhesion molecule 1
172	4685	NCAM2	Neural cell adhesion molecule 2
173	4780	NFE2L2	Nuclear factor erythroid 2-like 2
174	195727	Nhs	Nance-Horan syndrome
175	126205	NLRP	NOD-like receptor
176	23530	NNT	Nicotinamide Nucleotide Transhydrogenase
177	4843	NOS2	Nitric oxide synthase 2
178	4846	NOSIII	Nitric Oxide 3
179	4878	NPPA	Natriuretic peptide A
180	4973	OLR1	Oxidized low density lipoprotein receptor 1

181	4978	OPCML	Opioid binding protein/cell adhesion molecule like
182	100820719	OPGB	Osteoprotegerin
183	64805	P2RY12	Purinergic receptor P2Y12
184	6596	PA-1	Plasminogen activator inhibitor 1
185	56288	PARD3	Par-3 family cell polarity regulator
186	5101	PCDH9	Protocadherin 9
187	5111	PCNA	Proliferating cell nuclear antigen
188	5122	PCSK1	Proprotein convertase subtilisin/kexin type 1
189	255738	PCSK9	Proprotein convertase subtilisin/kexin type 9
190	5156	PDGF	Platelet-derived growth factor
191	5175	PECAM1	Platelet and endothelial cell adhesion molecule 1
192	5243	P-GP	P Glycoprotein
193	221692	PHACTR1	Phosphatase and actin regulator 1
194	5245	PHB	Prohibitin
195	5322	PLA2G5	Phospholipase A2 group V
196	5327	PLAT	Plasminogen activator, tissue type
197	5348	PLIN	Perilipin gene
198	80339	PNPLA3	Patatin like phospholipase domain containing 3
199	5444	PON	Paraoxonase
200	5444	PON1	Paraoxonase 1
201	8613	PPAP2B	Phosphatidic acid phosphatase type 2B
202	5465	PPARA	Peroxisome proliferator activated receptor alpha
203	5468	PPARG	Peroxisome proliferator activated receptors
204	5468	PPARgamma	Peroxisome proliferator activated receptor gamma
205	10544	PROCR	Protein C receptor
206	100861193	PROLACTIN	PROLACTIN protein
207	354	PSA	Prostate specific antigen

208	11122	PTPRT	Protein tyrosine phosphatase, receptor type T
209	5806	PTX3	Pentraxin 3
210	79874	RABEP2	Rabaptin, RAB GTPase binding effector protein 2
211	177	RAGE	Advanced glycosylation end-product specific receptor
212	56729	RETN	Resistin
213	4919	ROR1	Receptor tyrosine kinase like orphan receptor 1
214	6196	RPS6KA2	Ribosomal protein S6 kinase A2
215	6198	RPS6KB1	Ribosomal protein S6 kinase B1
216	57521	RPTOR	Regulatory associated protein of MTOR complex 1
217	6402	SELL	Selectin L
218	23411	SIRT1	Sirtuin 1
219	6583	SLC22A4	Solute carrier family 22 member 4
220	6532	SLC6A4	Solute carrier family 6 member 4
221	100308165	SMA	Semispinalis lean area
222	6621	SNAPC4	Small nuclear RNA activating complex polypeptide 4
223	6720	SREBF1	sterol regulatory element binding transcription factor 1
224	6774	STAT3	Signal transducer and activator of transcription 3
225	6943	TCF21	Transcription factor 21
226	6934	TCF7L2	Transcription factor 7 like 2
227	7021	TFAP2B	Transcription factor AP-2 beta
228	7056	THBD	Thrombomodulin
229	2147	Thrombin	Thrombin
230	7099	TLR4	Toll like receptor 8
231	81615	TMEM163	Transmembrane protein 163
232	7124	TNF	Tumor necrosis factor alpha
233	7137	TNNI3	Cardiac Troponin I

234	51086	TNNI3K	TNNI3 interacting kinase
235	7139	TNNT2	Troponin T2, cardiac type
236	7173	TPO	Thyroid peroxidase
237		TRAF6	tumor necrosis factor receptor-associated factor 6
238	193034	TRPV1	Transient receptor potential cation channel
239	54970	TTC12	Tetratricopeptide repeat domain 12
240	158219	TTC39B	Tetratricopeptide repeat domain 39B
241	10911	UTS2	Urotensin II
242	7412	VCAM1	Vascular cell adhesion molecule 1
243	7421	VDR	Vitamin D receptor
244	22340	VEGF	Vascular endothelial growth factor
245	7422	VEGFA	Vascular endothelial growth factor A
246	7423	VEGFB	vascular endothelial growth factor B
247	10135	VF	Visfatin
248	7431	VIM	Vimentin
249	619537	VV	Varicose veins
250	7450	VWF	Von Willebrand factor
251	54361	WNT4	wingless-type MMTV integration site family, member 4
252	7474	WNT5A	Wnt family member 5A
253	51741	WWOX	WW domain containing oxidoreductase

Annexure V

List of Gens with High BC and Degree values

GENE NAME	Degree	Betweeness

INS	141	0.17342958
ALB	124	0.08819711
TNF	105	0.0567376
IL-6	111	0.04942646
VEGFA	94	0.04888256
MAPK3	82	0.04848889
STAT3	71	0.03587785
IL8	82	0.03096708
CAT	51	0.03080475
IL1B	68	0.02138138
ADIPOQ	64	0.02125903
MAPK8	72	0.01996994
PPARG	70	0.01935642
SIRT1	50	0.01930777
CCL2	73	0.01811743
CRP	74	0.018104444
AGT	50	0.01663314
ESR1	54	0.01555875
APOB	58	0.01504999
LEP	69	0.01389817
IL10	67	0.01159901
APOE	68	0.011390959
PTGS2	63	0.011091293
MMP9	63	0.011028796
ICAM1	68	0.01073596
ACE	57	0.00948131
TLR4	59	0.00853086
FGF2	54	0.00749462
VCAM1	62	0.00611796
MMP2	50	0.00479683
LDLR	50	

Annexure VI

List of TEST networks

Number of genes omitted	Genes omitted	Top 6 nodes with largest BC and degree	Hub node not retained in test network	Number of nodes in the test networks belonging to the backbone	Accuracy of backbone	Overall accuracy	NETWORK
1	MMP2	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	VCAM1	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	FGF2	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	TLR4	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	ACE	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	ICAM1	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	MMP9	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	PTGS2	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	APOE	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	IL10	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	LEP	INS,ALB,IL6,TNF,VEGFA		5	1		1
1	APOB	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	ESR1	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	AGT	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	CRP	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	CCL2	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	SIRT1	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	PPARG	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	MAPK8	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	ADIPOQ	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	IL1B	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	CAT	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	IL8	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	STAT3	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	MAPK3	INS,ALB,TNF,IL6,VEGFA		5	1		1
1	VEGFA	INS,ALB,IL6,TNF,IL8	VEGFA	4	0.8		1
1	IL-6	INS,ALB,TNF,VEGFA,IL8	IL-6	4	0.8		1
1	TNF	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
1	ALB	INS,TNF,VEFGA,IL6,MAPK3	ALB	4	0.8		1
1	INS	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
						0.97	
2	INS,MMP2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,VCAM1	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1

2	INS,FGF2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,TLR4	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,ACE	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,ICAM1	ALB,TNF,IL6,VEGFA,MAPK3	INS	4	0.8		1
2	INS,MMP9	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,PTGS2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,APOE	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,IL10	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,LEP	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,APOB	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,ESR1	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,AGT	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,CRP	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,CCL2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,SIRT1	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,PPARG	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,MAPK8	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,ADIPOQ	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,IL1B	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,CAT	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,IL8	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,STAT3	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	INS,MAPK3	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
2	ALB,MMP2	TNF,IL6,MAPK3,STAT3,IL8	ALB,INS,VEGFA	2	0.4		1
2	ALB,VCAM1	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,FGF2	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,TLR4	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,ACE	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,ICAM1	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,MMP9	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,PTGS2	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,APOE	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,IL10	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,LEP	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,APOB	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,ESR1	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,AGT	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,CRP	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,CCL2	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1

2	ALB,SIRT1	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,PPARG	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,MAPK8	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,ADIPOQ	INS,TNF,1L6,VEGFA,MAPK3	ALB	4	0.8		1
2	ALB,IL1B	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
2	ALB,STAT3	INS,TNF,IL6,MAPK3,VEGFA	ALB	4	0.8		1
2	ALB,MAPK3	INS,TNF,VEGFA,IL6,STAT3	ALB	4	0.8		1
2	TNF,MMP2	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,VCAM1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,FGF2	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,TLR4	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,ACE	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,ICAM1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,MMP9	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,PTGS2	INS,ALB,IL6,MAPK3,VEGFA	TNF	4	0.8		1
2	TNF,APOE	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,IL10	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,LEP	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,APOB	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNS,SIRT1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,CRP	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,AGT	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,ESR1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,CCL2	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,PPARG	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,MAPK8	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,ADIPOQ	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
2	TNF,IL1B	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.4		1
2	TNF,STAT3	INS,ALB,IL6,MAPK3,VEGFA	TNF	4	0.8		1
2	TNF,MAPK3	INS,ALB,IL6,MAPK3,STAT3	TNF	4	0.8		1
2	IL6,MMP2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,VCAM1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,FGF2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,TLR4	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,ACE	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,ICAM1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,MMP9	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,PTGS2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,APOE	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1

2	IL6,IL10	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,LEP	INS,ALB,TNF,VEGFA,MAPK3	IL6	2	0.4		1
2	IL6,APOB	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,ESR1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,AGT	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,CRP	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,CCL2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,SIRT1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,PPARG	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,MAPK8	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,ADIPOQ	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,IL1B	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
2	IL6,STAT3	INS,ALB,TNF,MPAK3,VEGFA	IL6	4	0.8		1
2	IL6,MAPK3	INS,ALB,TNF,VEGFA,STAT3	IL6	4	0.8		1
2	VEGFA,MMP2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,VCAM1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,FGF2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,TLR4	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,ACE	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,ICAM1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,MMP9	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,PTGS2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,APOE	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,IL10	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,LEP	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,APOB	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,ESR1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,AGT	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,CRP	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,CCL2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,SIRT1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,PPARG	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,MAPK8	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,ADIPOQ	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,IL1B	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
2	VEGFA,STAT3	INS,ALB,TNF,MAPK3,IL6	VEGFA	4	0.8		1
2	VEGFA,MAPK3	INS,ALB,TNF,IL6,STAT3	VEGFA	4	0.8		1
						0.8	
3	INS,MMP2,VCAM1	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1

3	INS,FGF2,TLR4	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,ACE,ICAM1	ALB,TNF,IL6,VEGFA,MAPK3	INS	4	0.8		1
3	INS,MMP9,PTGS2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,APOE,IL10	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,LEP,APOB	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,ESR1,AGT	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,CRP,CCL2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,SIRT1,PPARG	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,MAPK8,ADIPOQ	ALB,IL6,TNF,MAPK3,VEGFA	INS	4	0.8		1
3	INS,IL1B,STAT3	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
3	INS,ADIPOQ,MAPK3	ALB,IL6,TNF,VEGFA,STAT3	INS	4	0.8		1
3	ALB,MMP2,VCAM1	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,FGF2,TLR4	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,ACE,ICAM1	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,MMP9,PTGS2	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,APOE,IL10	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
3	ALB,LEP,APOB	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,ESR1,AGT	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,CRP,CCL2	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
3	ALB,SIRT1,PPARG	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
3	ALB,MAPK8,ADIPOQ	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
3	ALB,IL1B,STAT3	INS,TNF,VEGFA,IL6,MAPK3	ALB	4	0.8		1
3	ALB,ADIPOQ,MAPK3	INS,TNF,IL6,VEGFA,STAT3	ALB	4	0.8		1
3	TNF,MMP2,VCAM1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,FGF2,TLR4	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,ACE,ICAM1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,MMP9,PTGS2	INS,ALB,IL6,MAPK3,VEGFA	TNF	4	0.8		1
3	TNF,APOE,IL10	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,LEP,APOB	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,ESR1,AGT	INS,ALB,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,CRP,CCL2	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,SIRT1,PPARG	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,MAPK8,ADIPOQ	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
3	TNF,IL1B,STAT3	INS,ALB,IL6,MAPK3,VEGFA	TNF	4	0.8		1
3	TNF,ADIPOQ,MAPK3	INS,ALB,IL6,VEGFA,STAT3	TNF	4	0.8		1
3	VEGFA,MMP2,VCAM1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,FGF2,TLR4	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,ACE,ICAM1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,MMP9,PTGS2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1

3	VEGFA,APOE,IL10	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,LEP,APOB	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,ESR1,AGT	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,CRP,CCL2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,SIRT1,PPARG	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,MAPK8,ADIPOQ	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,IL1B,STAT3	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
3	VEGFA,ADIPOQ,MAPK3	INS,ALB,TNF,IL6,STAT3	VEGFA	4	0.8		1
3	IL6,MMP2,VCAM1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,,FGF2,TLR4	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,ACE,ICAM1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,MMP9,PTGS2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,APOE,IL10	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,LEP,APOB	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,ESR1,AGT	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,CRP,CCL2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,SIRT1,PPARG	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,MAPK8,ADIPOQ	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
3	IL6,IL1B,STAT3	INS,ALB,TNF,MAPK3,VEGFA	IL6	4	0.8		1
3	IL6,ADIPOQ,MAPK3	INS,ALB,TNF,VEGFA,STAT3	IL6	4	0.8		1
						0.8	
4	INS,MMP2,VCAM1,FGF2	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,TLR4,ACE,ICAM1	ALB,TNF,IL6,VEGFA,MAPK3	INS	4	0.8		1
4	INS,MMP9,PTGS2,APOE	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,IL10,LEP,APOB	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,ESR1,AGT,CRP	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,CCL2,SIRT1,PPARG	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,MAPK8,ADIPOQ,IL1B	ALB,TNF,IL6,MAPK3,VEGFA	INS	4	0.8		1
4	INS,STAT3,MAPK3,CCL2	ALB,TNF,IL6,VEGFA,IL8	INS	4	0.8		1
4	ALB,MMP2,VCAM1,FGF2	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,TLR4,ACE,ICAM1	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,MMP9,PTGS2,APOE	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,IL10,LEP,APOB	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,ESR1,AGT,CRP	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,CCL2,SIRT1,PPARG	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,MAPK8,ADIPOQ,IL1B	INS,TNF,IL6,VEGFA,MAPK3	ALB	4	0.8		1
4	ALB,STAT3,MAPK3,CCL2	INS,TNF,IL6,VEGFA,IL8	ALB	4	0.8		1
4	TNF,MMP2,VCAM1,FGF2	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
4	TNF,TLR4,ACE,ICAM1	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1

4	TNF,MMP9,PTGS2,APOE	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
4	TNF,IL10,LEP,APOB	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
4	TNF,ESR1,AGT,CRP	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
4	TNF,CCL2,SIRT1,PPARG	INS,ALB,IL6,VEGFA,MAPK3	TNF	4	0.8		1
4	TNF,MAPK3,ADIPOQ,IL1B	INS,ALB,IL6,VEGFA,STAT3	TNF	4	0.8		1
4	TNF,STAT3,MAPK3,CCL2	INS,ALB,IL6,VEGFA,IL8	TNF	4	0.8		1
4	IL6,MMP2,VCAM1,FGF2	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,TLR4,ACE,ICAM1	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,MMP9,PTGS2,APOE	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,IL10,LEP,APOB	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,ESR1,AGT,CRP	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,CCL2,SIRT1,PPARG	INS,ALB,TNF,VEGFA,MAPK3	IL6	4	0.8		1
4	IL6,MAPK3,ADIPOQ,IL1B	INS,ALB,TNF,VEGFA,STAT3	IL6	4	0.8		1
4	IL6,STAT3,MAPK3,CCL2	ALB,TNF,IL6,VEGFA,IL8	IL6	4	0.8		1
4	VEGFA,MMP2,VCAM1,FGF2	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,TLR4,ACE,ICAM1	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,MMP9,PTGS2,APOE	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,IL10,LEP,APOB	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,ESR1,AGT,CRP	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,CCL2,SIRT1,PPARG	INS,ALB,TNF,IL6,MAPK3	VEGFA	4	0.8		1
4	VEGFA,MAPK3,ADIPOQ,IL1B	INS,ALB,TNF,IL6,STAT3	VEGFA	4	0.8		1
4	VEGFA,STAT3,MAPK3,CCL2	INS,ALB,TNF,IL6,IL8	VEGFA	4	0.8		1
						0.8	