Thesis- The Hub Design to the common genes and Their Interactions in pulmonary tuberculosis

Submitted By

Belayet Hossan Billal
ID: 193-35-492
Department of SWE
Daffodil International University

Supervised By

Dr. Md. Fazla Elahe
Assistant Professor & Associate Head
Department of SWE
Daffodil International University

DAFFODIL INTERNATIONAL UNIVERSITY

DHAKA, BANGLADESH

ACKNOWLEDGEMENT

First, I express my heartiest thanks and gratefulness to almighty God for His divine blessing makes it possible to complete the final year project/internship successfully.

I am really grateful and wish profound indebtedness to **Md. Fazla Elahe Assistant Professor & Associate Head**, Department of SWE Daffodil International University, Dhaka. Deep Knowledge & keen interest of our supervisor in the field of "*Deep Learning*" to carry out this project. His endless patience, scholarly guidance, continual encouragement, constant and energetic supervision, constructive criticism, valuable advice, reading many inferior drafts and correcting them at all stages have made it possible to complete this project.

Additionally, I would like to express my heartiest gratitude to the Supervisor and Head**,** Department of SWE, for his kind help to finish our project and also to other faculty members and the staff of SWE department of Daffodil International University.

I would like to thank our entire course mate in Daffodil International University, who took part in this discussion while completing the course work.

Finally, I must acknowledge with due respect the constant support and patients of my parents.

APPROVAL

This thesis titled on "The Hub Design to the common genes and Their Interactions in pulmonary tuberculosis", submitted by **Belayet Hossan Billal (ID: 193-35-492)** to the Department of Software Engineering, Daffodil International University has been accepted as satisfactory for the partial fulfillment of the requirements for the degree of Bachelor of Science in Software Engineering and approval as to its style and contents.

BOARD OF EXAMINERS

---------- **Chairman**

Dr. Imran Mahmud
Head and Associate Professor
Department of Software Engineering
Faculty of Science and Information Technology
Daffodil International University

Fazla Elahe 16.07.23
---------- **Internal Examiner 1**

Dr. Md Fazla Elahe
Assistant Professor & Associate head
Department of Software Engineering
Faculty of Science and Information Technology
Daffodil International University

---------- **Internal Examiner 2**

Tapushe Rabaya Toma
Assistant Professor
Department of Software Engineering
Faculty of Science and Information Technology
Daffodil International University

---------- **External Examiner**

Prof. Dr. Md. Liakot Ali
Professor
Bangladesh University of Engineering and Technology (BUET)

DECLARATION

I hereby declare that this Thesis has been done by us under the supervision of, **Dr. Md. Fazla Elahe Assistant Professor & Associate Head, Department of SWE** Daffodil International University. I also declare that neither this Thesis nor any part of this project has been submitted elsewhere for award of any degree or diploma.

Fazla Elahe

Supervised by:

Md. Fazla Elahe
Assistant Professor & Associate Head
Department of SWE
Daffodil International University

Belayet

Submitted by:

Belayet Hossan Billal
ID: 193-35-492
Department of SWE
Daffodil International University

©Daffodil International University 4

ABSTRACT

The leading causes of death and disability worldwide are pulmonary tuberculosis (PTB) and non-communicable diseases (NCDs), such as lung cancer (LC), diabetes mellitus (DM), Parkinson's disease (PD), silicosis (SL), chronic kidney disease (CKD), cardiovascular disease (CDV), and rheumatoid arthritis (RA). Millions of individuals worldwide suffer to these illnesses every year. There was a connection between each of the disorders. Any patient with one of these disorders is at increased risk for developing another. The genetic relationships between PTB and NCDs are presented in this study. And pinpoint the genes that are shared by many different diseases. Protein-protein interaction (PPI), gene regulatory network (GRN), enrichment analysis, co-expression, and physical interaction can all be used to develop effective treatments for disease. The intrinsic functions of the shared genes were uncovered by employing enrichment techniques. It shows a robust connection between the shared genes and the emergence and dissemination of PTB. To separate disease-specific genes from common ones, researchers use a variety of processing and filtering techniques. TNF, IL10, NLRP3, IL18, IFNG, HMGB1, CXCL8, IL17A, and NFKB1 were among the nine genes shared by PTB and NCDs. Four of the five hub genes (NFKB1, TNF, CXCL8, NLRP3, and IL10) were associated with the three drugs. This bioinformatics research may help researchers better understand the causes of PTB and NCDs, and eventually find effective ways to treat them.

Contents

LIST OF FIGURES

LIST OF TABLES

CHAPTER 1

INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by bacillus Mycobacterium tuberculosis. Every year, more than a million people die from tuberculosis (TB). Smoking, use of alcohol, and diabetes can increase the risk of TB by suppressing the immune system [1]. The World Health Organization (WHO) reports that 10 million people contracted TB in 2017, and 1.6 million died from it, including 0.3 million HIV-positive people [2]. In 2019, 3.6% of people in Bangladesh were infected with TB, and approximately 10.0 million people were infected. COVID-19 displaced TB as the leading worldwide infectious illness in 2020 [3]. Additionally, undernutrition accounted for one-quarter of all tuberculosis cases worldwide [4].

TB can cause the immune system to break down, making an individual more susceptible to non-communicable diseases (cardiovascular diseases, diabetes, cancer, and chronic respiratory diseases), having the highest worldwide mortality and morbidity rates. Additionally, people with TB are more likely to have problems with their mental health. [5, 6]. It causes more than 70% of global deaths, and low- and middle-income countries must deal with a disproportionate number of NCDs [7].

One of the primary diseases that significantly increases the rate of mortality worldwide is cancer [8]. It is the most significant cause of death worldwide, accounting for 15 million new cancer cases and 8.2 million deaths yearly. Lung cancer (LC) is the most prevalent cancer in men and women and the leading cause of cancer death. Worldwide 1.8 million or more people die from lung cancer yearly [9]. The abnormality of the Fragile Histidine Triad (FHIT) gene is involved in lung cancer in people with pulmonary tuberculosis (PTB) [10]. Silicosis (SL) is also a risk factor for increased TB. It is a type of pneumonitis that affects the lungs, caused by inhaling high volumes of silica dust. SL patients have risk to develop PTB more than those without the disease. Inhalation of crystalline silica dust can increase the risk of LC and mycobacterial infections. CKD and RA are also associated with silica [11, 12]. In 2016, CKD was the 11th major cause of death worldwide. Patients with CKD lose their renal function then the symptoms appear [13]. CKD patients are more likely to develop TB. According to the National Institute for Excellence in Health and Care, the relative risk of developing active TB in patients with CKD at any stage is 10 to 25%. CKD affects up to 16% of the world's population and at least 2% of patients requiring dialysis. Dialysis increases the risk of TB compared to patients who are not requiring dialysis [14, 15]. RA is a progressive autoimmune illness that begins in the small joints and spreads to the larger joints (joints are often destroyed, and ligaments and tendons get weaker), kidneys, heart, and lungs [16]. We aimed to examine the genetic relationship between

Pulmonary Tuberculosis, lung cancer, diabetes mellitus, Parkinson's disease, silicosis, chronic kidney disease, cardiovascular disease, and rheumatoid arthritis. A total of nine common genes were discovered. The main contributions of this study are as follows:

1. To examine the genetic relationship among eight overlaying non-communicable diseases such as PTB, LC, DM, PD, SL, CKD, CVD, and RA and find out hub genes from the common genes.

2. To discover drug components based on P-value and adjusted P-value to identify drug components those are connected with the hub genes.

CHAPTER 2

Keyword

Pulmonary Tuberculosis, lung cancer, Diabetes mellitus, Parkinson's disease, Silicosis, Chronic kidney disease, cardiovascular disease, and Rheumatoid arthritis.

CHAPTER 3

Literature Review

Around 0.5-1.0% of the global population is suffering. RA becomes more common with age, and women have a more considerable risk than males [17]. RA patients have an elevated chance of contracting life-threatening infections, cancer, and cardiovascular disease [18]. Cancer is one of the three main reasons people die from RA, along with infections and cardiovascular disease [19]. PA is a neurodegenerative disorder that gradually becomes more severe and affects both physical and mental functions [20]. About 6.9 million people affected in 2015, and 14.2 million will likely be affected by it by 2040. The symptoms of PD develop over time but may not be noticeable until the disease has progressed significantly [21]. CVD is the leading cause of death worldwide, and its prevalence keeps increasing compared to the last few decades [22]. Comorbidities like obesity, abnormal lipid profiles, and insulin resistance are often linked to CVD [23]. Besides, hyperlipidemia, diabetes, hypertension, and smoking are linked to CKD [24]. Diabetes mellitus, a global epidemic that reveals itself when glucose levels in the blood rise too high, and kidney function declines, is caused by a failure to create or properly utilize insulin. It was calculated that the disease directly caused 1.5 million deaths in 2019. This disease's incidence is rising rapidly in low and middle-income economies [25].

In past years, observational evidence of a link between cancer and tuberculosis has developed [26]. A study identifies miRNA expression patterns in serum in Egyptian people with LC, TB, and pneumonia. miR-182 and miR-197 levels were high in LC and TB patients, and miR-21, miR-155, and miR-197 levels were high in LC, TB, and pneumonia patients [27]. In patients with CKD, the risk of TB increases in CKD stage 3, and CKD stage 5 is higher than in the number of dialysis patients [28]. In older patients, renal impairment is a common side effect of anti-TB medication [29]. A higher cancer risk at ten different sites has been linked to tuberculosis. Low-resource countries disproportionately bear the cancer burden linked to TB [30]. Another study extracted 13 common genes (IL6, TLR4, TNF, CRP, CCL2, IL10, IL1B, TGFB1, ADIPOQ, ACE, VEGFA, IL1RN, HIF1A) among chronic obstructive pulmonary disease, diabetes mellitus, cirrhosis, ischemic heart disease, ischemic stroke, tuberculosis, obesity from genetic PPI, enrichment analysis, gene regulatory network, co-expression, and physical interaction. And four significant genes (TNF, IL6, IL10, and IL1B) were used to explore drug design and treatment from protein disease interaction and protein chemical interaction network [31]. From a systematic review, people with hematologic, head and neck, or lung cancer in the US had a 9-fold higher chance of getting active tuberculosis. But most investigations failed to quantify how long they followed up with participants and could not estimate annual TB cases risk after a cancer diagnosis or risk [32]. A study showed 2.79% of people with LC had previously

had TB. These individuals had a higher risk of dying within three years of being diagnosed with LC than those without a TB history. But this study used a claimed database and lacked pulmonary function, laboratory, and lung cancer genetic data [33]. In a study, 11 common genes- TNF, IL6, ICAM1, TGFB1, BDNF, AGT, ADIPOQ, CRP, PON1, SOD1, and IL8 were found in 4 diseases (diabetes, kidney disease, stroke, and anxiety). Protein-protein interaction & regulatory interaction network was an analyst from the 11 common genes. Among the 11 genes, seven significant genes (TGFB1, TNF, PON1, CRP, ICAM1, CXCL8, and AGT) were used for gene co-expression network & Physical interaction pathway [34]. In another retrospective study, patients with RA are more likely to get tuberculosis, which could result from anti-TNF treatments but very few TB patients constituted a serious constraint that contributed greatly to the possibility of bias [35]. A study finds growing evidence that individuals with - NCDs represent a high-risk group for developing active TB [36]. The current quantitative analysis showed that infection might make the chance of getting PD higher, and the significance of the relationship differed based on the particular pathogens but the number of qualified studies was small and there are different kinds of infections [37]. The association between type 2 diabetes and PD has become clear, but the underlying molecular pathways are still unknown [38]. CVD is the alarming rise of DM and its significant consequences [39]. Both CVD and PD share biological processes, including inflammation, insulin resistance, oxidative stress, and lipid metabolism [40].

Several studies only looked at a single population, so their outcomes only apply to some people. Lifestyle, environmental factors, behaviors, and dietary information can cause noncommunicable illnesses. In some studies, these data are absent in the dataset. Some studies are designed using a cross-sectional methodology. It might be challenging to determine whether or not the diseases are connected because it is difficult to make a straight cause and-effect inference. After all, the scenario could have had different results at different times. Some longitudinal study analyses limited health centers and included little patient information.

CHAPTER 4

RESEARCH METHODOLOGY

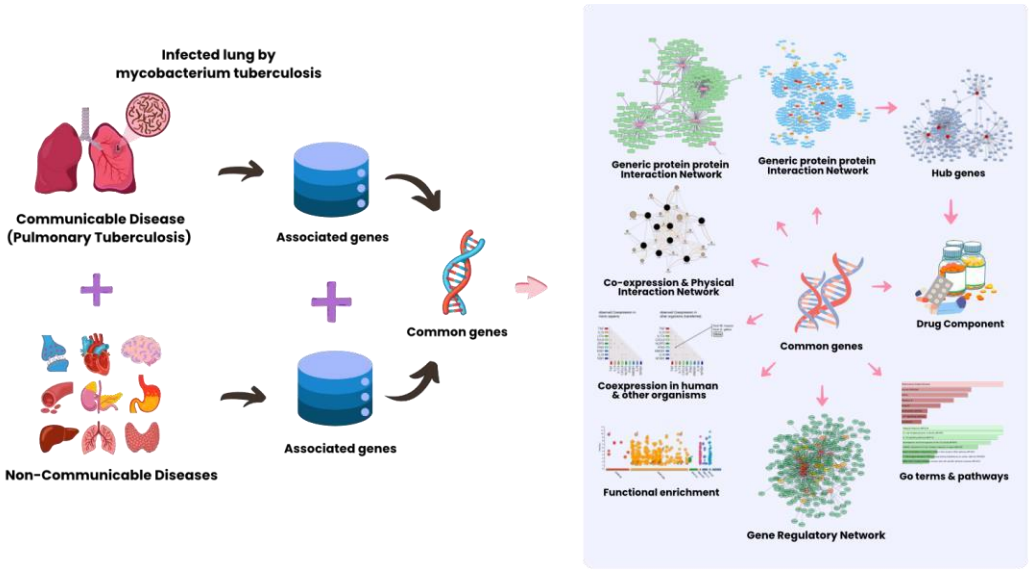


Figure 1. The process and methodology used in this study are depicted in Figure 1. Common genes were identified by searching the NCBI gene database. The bioinformatics study made use of widely studied genes. Different analysis tools are used for identifying GO terms, pathways, protein-protein interactions, transcription factors, microRNAs, and hub genes.

2.1 Gene collection

National Center for Biotechnology Information (NCBI) online gene database has been used to collect common genes (https://www.ncbi.nlm.nih.gov/gene/). It is a branch of the National Library of Medicine at the National Institutes of Health established to develop molecular biology information systems. This database holds gene information. It has 32928347 records of the gene [41]. These genes were gathered just for Homo sapiens in this study, which is intended for developing the drug for humans. The common genes were entered into Network Analyst (https://www.networkanalyst.ca/). Researchers can find relevant characteristics, patterns, functions, and relationships in complex gene expression data. It provides visual analytics experience for data analysis [42]. Drug designs were identified using various methods.

2.2. Construction of PPIs networks and identification of hub genes

PPIs play a central role in a variety of cellular and organismal processes, building the cellular framework to immunological defense and cellular communication [43]. Generic

PPI and Tissue-specific PPI (whole blood tissue) have been used to analyze protein-protein interaction networks. These two analyses were carried out with the help of a Network Analyst. Genetic PPI was performed by the STRING Interactome database with a 900-confidence score cutoff. The STRING database collects and combines information on protein-protein interactions, both structural and functional [44]. STRING confidence scores indicate the likelihood of finding related proteins in the same KEGG pathway [45]. The Differential Net database has been used to examine tissue-specific PPI. The Differential Net database gives differential interactomes for more than 29 human tissues by scoring data of PPIs. It reveals tissue-specific protein functions, processes, and phenotypes. [46]. In tissue-specific PPI, whole blood cell has been counted with filter 15.0. The acquired genetic PPIs are analyzed using Cystoscope (https://cytoscape.org/) to provide a clearer graphic illustration of the network to explore biological interaction. It is a widely used open-source program for visualizing gene and protein interaction networks, among other types of biological networks [47]. To identify the hub genes cynophobes plugin (http://apps.cytoscape.org/apps/cytohubba) has been used based on the topological analysis. cynophobes ranking network components based on their network features. It provides topological analyses and centralities. Degree method, Maximum Neighborhood Component (MNC), Edge Percolated Component (EPC), Density of Maximum Neighborhood Component (DMNC), Maximal Clique Centrality (MCC), Eccentricity, Bottleneck, Closeness methods were implemented to determine the significance of nodes. From those methods, direct neighborhood, shortest paths and percolated connectivity were analyzed. Degree, MNC, DMNC, and MCC find out the neighborhood of the vertex. Closeness, Betweenness, bottleneck, Eccentricity, stress find out the shortest paths. And EPC find the percolated connectivity.

2.3. Gene regulatory networks (GRN)

GRN offers a mathematical framework for describing the intricate interaction between gene transcription, genes, and gene products [49]. It was analyzed by gene-miRNA interaction and TF-gene interaction. miRTarBase database has been used in gene-miRNA interaction. miRTarBase provide exhaustive details on experimentally validated miRNA– target interactions. The database contains more than 13,404 validated MTIs [50]. And ENCODE

database has been used in TF-gene interaction. That two analyses were also done by the Network analysis online tool (www.NetworkAnalyst.ca).

2.4 Gene Ontology and pathway enrichment analysis

Gene set enrichment analysis is a statistical and computational method to determine if a group of genes exhibits statistical importance across a range of biological contexts [51]. Gene Ontology (GO) offers organized, controlled vocabularies and categories that cover multiple areas of molecular and cellular biology of a gene. It offers three distinct areas of molecular biology - biological process, molecular function, and cellular component to identify the features of the gene. [52]. For pathway analysis, Bio Carta, KEGG, WikiPathways, and Reactome databases were employed [53, 54]. The results from the databases and GO terms are implemented using Enrich (https://maayanlab.cloud/Enrichr/). It offers multiple methodologies for calculating gene set enrichment, and the results can be viewed in a number of interactive ways. It uses different machine-learning methods [55]. g: profiler is also used for enrichment analysis. It is frequently used to convert gene identifiers, map genes to their orthologs, and find biological groups enriched in gene lists [56].

2.5 Co-expression Network and Physical Interaction Network

Co-expression Network and Physical Interaction Network have been done by a Cystoscope plugin - Gene MANIA (https://apps.cytoscape.org/apps/GeneMania). Gene Mania's interface allows for a wide range of inquiries about genomic, proteomic, and gene function information. It measures gene function hypotheses, list analysis, and gene prioritization for functional experiments [57]. Co-expression result based on protein co-regulation and RNA expressions were implemented using string database (https://string-db.org/).

2.6 Identify drug candidate

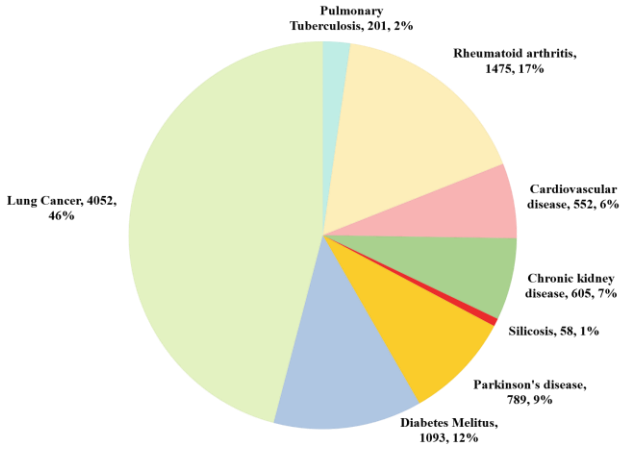
The most important part of the ongoing research is finding the drug molecules among the 8 diseases. Using the Drug Signatures database (DSigDB), which hold 22527 gene sets with 17389 distinct compounds encompassing a total of 19531 genes. It holds a group of drugs- and small-molecule-related gene sets based on data about how gene expression changes because of drugs [58]. The Enrich platform (https://amp.pharm.mssm.edu/Enrichr/) is used to get into the DSigDB database.

CHAPTER 5

RESULTS AND ANALYSIS

3.1 Gene collection:

A total of 8825 genes were discovered from the gene database. After filtering the genes, nine common genes were found. Those genes are - TNF (Entrez ID: 7124), IL10 (Entrez ID: 3586), NLRP3 (Entrez ID: 114548), IL18 (Entrez ID: 3606), IFNG (Entrez ID: 3458), HMGB1 (Entrez ID: 3146), CXCL8 (Entrez ID: 3576), IL17A (Entrez ID: 3605), and



NFKB1 (Entrez ID: 4790) for discover- PPIs network, hub genes, GO and pathway analysis, and GRN. The number of genes for Homo sapiens is illustrated in figure 2. And the list of common genes is depicted in table 1.

Figure 2. The pie chart shows the eight disease genes in different segments. The number beside the disease name represents the gene number and percentage.

Table1. Common gene lists between the diseases. Table1. Common gene lists between the diseases.

Table1. Common gene lists between the di 1Table1. Common gene lists between the diseases.

Serial	Disease Name	Amount	Genes
1	PTB, CKD, CVD, DM, LC, PD, RA, SL	9	IL18, IL10, HMGB1, IL17A, ……, NLRP3, CXCL8
2	CKD, CVD, DM, LC, PD, RA, SL	6	GSTP1, LGALS3, ACE, IL1A, HMOX1, TP53

3	CKD, CVD, DM, LC, PD, PTB, RA	17	APOE, TNFRSF1A, AGER, ……, MMP9, ADIPOQ
4	CKD, CVD, DM, LC, PTB, RA, SL	2	TGFB1, IL1RN

5	CKD, CVD, DM, PD, PTB, RA, SL	1	HLA-DRB1
6	CKD, DM, LC, PD, PTB, RA, SL	1	NEWENTRY
7	CVD, DM, LC, PD, PTB, RA, SL	1	IL1B
8	CKD, CVD, DM, LC, PD, RA	30	MMP2, NFE2L2, HP, VEGFA, ……, IGF2, VCAM1
9	CKD, CVD, DM, LC, RA, SL	1	IL12A
10	CKD, CVD, DM, LC, PTB, RA	10	LEP, MMP1, MMP3, STAT3, ……, FTO, MIF
11	CKD, CVD, DM, PD, PTB, RA	1	CCR5
12	CKD, CVD, LC, PD, RA, SL	1	FAS
13	CKD, CVD, LC, PD, PTB, RA	1	IL6R
14	CKD, DM, LC, PD, RA, SL	1	GSK3B
15	CKD, DM, LC, PD, PTB, RA	4	EGFR, ABCB1, TLR9, PTEN
16	CVD, DM, LC, PD, PTB, RA	4	SERPINA1, CTSB, CCL5, CCR2

17	CVD, DM, LC, PTB, RA, SL	1	IL4
18	DM, LC, PD, PTB, RA, SL	1	NOS2
19	CKD, CVD, DM, LC, PD	4	SOD2, CYP1A1, PPARGC1A, UCP2

20	CKD, CVD, DM, LC, RA	30	EDN1, SERPINF1, CARD8, ……, PTGS1, CXCL16,
21	CKD, CVD, DM, LC, PTB	1	LCN2
22	CKD, CVD, DM, PD, RA	1	CP
23	CKD, CVD, LC, PD, RA	2	TRPV1, CFH
24	CKD, DM, LC, PD, RA	13	EP300, SIRT6, MIR223, NEAT1, ……, RAC1, BDNF
25	CKD, DM, LC, PD, PTB	1	SP1
26	CKD, DM, LC, RA, SL	1	SFTPD
27	CKD DM LC PTB RA	5	CD28, MIR146A, HLA-B, CTLA4, DDIT3
28	CKD LC PD RA SL	1	C3
29	CKD, LC, PD, PTB, RA	1	P2RX7
30	CKD, LC, PTB, RA, SL	1	CXCR2
31	CVD, DM, LC, PD, RA	12	NR4A2, TF, SIRT3, MIR132, ……, HFE, SERPINE1
32	CVD, DM, LC, RA, SL	2	PRDX4, HGF
33	CVD, DM, LC, PTB, RA	5	CXCL10, MBL2, STAT4, LEPR, CXCL12
34	CVD, LC, PD, PTB, RA	2	CR1, NOD2

35	DM, LC, PD, RA, SL	1	XIST
36	DM, LC, PD, PTB, RA	8	TAP2, CD4, TAP1, IL27, ……, MIR124-1, CCL3
37	DM, LC, PTB, RA, SL	1	IL12B
38	DM, PD, PTB, RA, SL	1	HLA-DQB1

39	CKD, CVD, DM, LC	15	SHBG, AGT, B2M, ELN, ……, PAPPA, SLC5A2
40	CKD, CVD, DM, PD	4	GH1, APP, FGG, SLC2A9
41	CKD, CVD, DM, RA	19	TNNT2, BGLAP, PTH, ……, FNDC5, MSTN, FGF23
42	CKD, CVD, LC, PD	1	SESN2
43	CKD, CVD, LC, RA	7	XDH, C5, PTGER2, SMAD3, ABCG2, SAA1, NOX4
44	CKD, CVD, PD, RA	1	NPPC
45	CKD, DM, LC, PD	4	GPNMB, NQO1, CYP27B1, TGM2
46	CKD, DM, LC, RA	25	PRKCB, PTPN2, ITGA2, ……, MIR161, LTA
47	CKD, DM, LC, PTB	2	MMP8, POSTN
48	CKD, DM, PD, RA	3	PON2, NGFR, MIR146B
49	CKD, LC, PD, RA	10	XIAP, TREM2, ERBB2, ……, HSPA5
50	CKD, LC, PD, PTB	2	IDO1, WFDC2
51	CKD, LC, RA, SL	1	MUC1
52	CKD, LC, PTB, RA	6	SFTPA1, C4B, RELA, JUN, FN1, LGALS9

53	CVD, DM, LC, PD	7	FGA, CDKN2A, ALDH2, ……, COMT, CTSL
54	CVD, DM, LC, RA	23	HSPD1, IRS1, PPBP, OLR1, ……, SERPINH1, GHSR
55	CVD, DM, LC, PTB	1	SOD3
56	CVD, DM, PTB, RA	1	S100A12
57	CVD, LC, PD, RA	6	MIR34A, ATG16L1, ESR2, MIR26A1, CLOCK, CEBPB
58	CVD, LC, RA, SL	2	FSTL1, EGR1
59	CVD, LC, PTB, RA	2	IRF1, CALCA
60	DM, LC, PD, RA	21	BCL2, SHH, MIR221, ……, PARP1, IL16, MEG3
61	DM, LC, RA, SL	1	FASLG
62	DM, LC, PTB, RA	13	COL1A1, FOXP3, IL23R, ……, IL2RA, IL37, CD274
63	DM, PD, PTB, RA	1	SLC11A1
64	LC, PD, RA, SL	2	CTNNB1, E2F1
65	LC, PD, PTB, RA	3	CXCR4, NCAM1, NFKBIA
66	LC, PTB, RA, SL	1	IL17F
67	CKD, CVD, DM	18	SERPINA12, MGP, APOL1, ……, FABP1, HBA1
68	CKD, CVD, LC	8	TIMP2, NEDD4L, DKK3, ……, ROCK1, CADM1
69	CKD, CVD, PD	1	EPHX2
70	CKD, CVD, RA	2	LDLR, CTSS

71	CKD, DM, LC	22	MIR20A, MIRLET7G, ……, CYP24A1, PRKCA
72	CKD, DM, RA	15	NPY, CASR, CX3CR1, ……, CD80, AMH, CCN3
73	CKD, LC, PD	5	MIR17HG, AQP1, COL6A3, CHIT1, GSTO1
74	CKD, LC, RA	35	BRD4, CYP3A5, JAK2, ……, MIR421, LECT2
75	CKD, LC, SL	1	ZEB1
76	CKD, PD, RA	1	ATXN2
77	CKD, PTB, RA	1	FCGR3A
78	CVD, DM, LC	19	ELANE, IL1F10, ……, MIR661, USF1, IGFBP4
79	CVD, DM, PD	10	SORL1, MANF, FGB, GLP1R, ……, TET2, GCG
80	CVD, DM, RA	16	MFGE8, ACP1, IL1R, ……, CD34, SFRP5, SH2B3
81	CVD, LC, PD	4	IL1R2, FTH1, DNMT3A, NRG1
82	CVD, LC, RA	17	IL24, MIR26B, RUNX1, DUSP1, ……, PKM, CXCL5
83	CVD, PD, RA	2	TAS2R38, LRRK2
84	CVD, PTB, RA	3	LILRB1, EBI3, TRAF1
85	DM, LC, PD	31	CYP2D6, MAOA, MFN2, ……, ADH1B, CYP2R1
86	DM, LC, RA	80	IRAK1, TEK, PDCD5, ……, PRRC2A, TGFBI, CSF2
87	DM, LC, SL	1	ENO2

88	DM, LC, PTB	1	CAMP
89	DM, PD, RA	9	BCHE, DRD3, MIR29B2, ……, IFNL1, GPBAR1
90	DM, PTB, RA	6	PTPN22, FCN1, HLA-DPB1, IL2, PRTN3, FCN3
91	LC, PD, RA	39	TRIB3, MIR193A, CIP2A, ……, MIR425, PSMB9
92	LC, PD, SL	1	MIR205
93	LC, PD, PTB	1	NORAD
94	LC, RA, SL	5	CASP1, FAM13A, MIR101-1, BBC3, S100A4

95	LC, PTB, RA	16	CD247, ALKBH5, ……, BTLA, CD1D, YY1
96	LC, PTB, SL	1	ATF3
97	PD, PTB, RA	1	TLR10
98	PTB, RA, SL	1	IFNGR1
99	CKD, CVD	5	VKORC1, FMO3, SERPING1, NR3C2, UMOD
100	CKD, DM	35	GP1BA, C1QTNF3, AHI1, ……, ENPP1, F12, G6PC3
101	CKD, LC	62	MIR200B, RBM10, SETDB1, ……, BCL11A, CA1
102	CKD, PD	9	LONP1, RTN3, ITGA8, ……, SLC11A2, RGMA
103	CKD, RA	14	STAT5A, WARS1, CCL17, UBD, ……, MFAP4
104	CKD, PTB	1	HLA-A

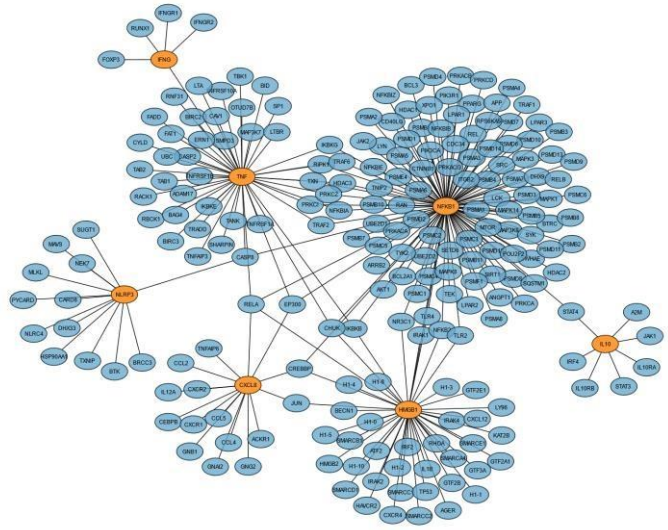
105	CVD, DM	29	SELL, GIPR, NRG4, APOA2, ……, UCP1, CAPN10
106	CVD, LC	37	MIR630, PTGER1, CA9, ……, INHBC, KDM5D
107	CVD, PD	10	PAWR, ARSA, DRD4, ……, BACE1AS, SLC6A3
108	CVD, RA	16	IL18RAP, CCL23, MIA3, ADAMTS4, ……, LRPAP1
109	DM, LC	143	AQP9, BRCA1, RUNX3, ……, HMGA1, RPS6KB1
110	DM, PD	19	ISM1, POLG, UNC13B, ……, PARL, DCC, RAB8A
111	DM, RA	44	MEFV, A2M, ARAP1, ……, PTPRS, METRNL
112	DM, PTB	2	KIR2DS1, TLR6
113	LC, PD	143	NTSR1, SLC8A1, ADH5, ……, BECN1, ASCL1, SRF
114	LC, RA	333	CD44, KCNMA1, ITGA5, ……, MIR212, MIR375
115	LC, SL	4	DSP, MUC16, SCGB1A1, MIRLET7I
116	LC, PTB	14	LEC4M, GCLC, ……, MIR196B, WTAP, METTL3
117	PD, RA	30	RIT2, TNFRSF9, BST1, ……, DYRK1A, SEMA5A
118	PD, PTB	1	TGM6
119	RA, SL	1	ZC3H12A
120	PTB, RA	11	ITGAX, MC3R, ……, HLA-DQB2, IFN1@

3.2 Construction of PPI networks and identification of hub genes

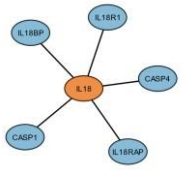
Generic PPI with STRING Interactome database analyzes protein-protein interaction. This analysis extracts two subnetworks. Subnetwork1 has 214 blue colored protein and 7 genes (NFKB1, TNF, HMGB1, NLRP3, CXCL8, IFNG, IL10) which color is blue shown in figure 3(a). Figure 3(b) has one highlighted yellow-colored gene (IL18), which interacted with five proteins (blue). RELA is the highest connected protein with CXCL8, HMGB1, NFKBI, and TNF genes. CXCL8, HMGB1, NFKBI, and TNF From generic PPI, five significant hub genes (TNF, NFKB1, HMGB1, CXCL8, NLRP3) were identified according to their degree value. Table 1 shows that NFKB1 has the highest degree value- 115, a 47-degree value for TNF, HMGB1 had a 44-degree value, and CXCL8 and NLRP3 had 16 and 13-degree values, respectively. Figure 4 demonstrates the hub protein with other interacted proteins from the generic PPIs network. Figure 5 represents the tissue-specific PPI network with four subnetworks. It was analyzed by whole blood tissue. Figure 5, 5(a) depicts subnetwork 1 with five genes (CXCL8, NFKB1, TNF, IFNG, and, IL10) which are connected with 165 proteins (green). The gene is colored pink. Subnetworks 2, 3, and 4 have one gene (pink)- HMGB1, NLRP3, and IL18, respectively. Subnetwork 2 has 28 proteins. Six proteins are connected with the gene in subnetwork3. Subnetwork4 has three proteins.

Table 2. Analyzing topological findings for the best-performing hub genes.

Gene	Betweenness	Closeness	Degree	Stress
NFKB1	37150.57	156	115	150398
TNF	15364.87	105.1167	47	128340
HMGB1	13907.83	118.6667	44	22612
CXCL8	5168.733	81.6	16	16024
NLRP3	5124	76.6	13	6684



(a) Subnetwork1



(a) Subnetwork2

Figure 3. Generic PPIs network for the eight diseases. Yellow seeds represent common genes, and edges indicate the connections between the protein. The proteins are marked with orange color.

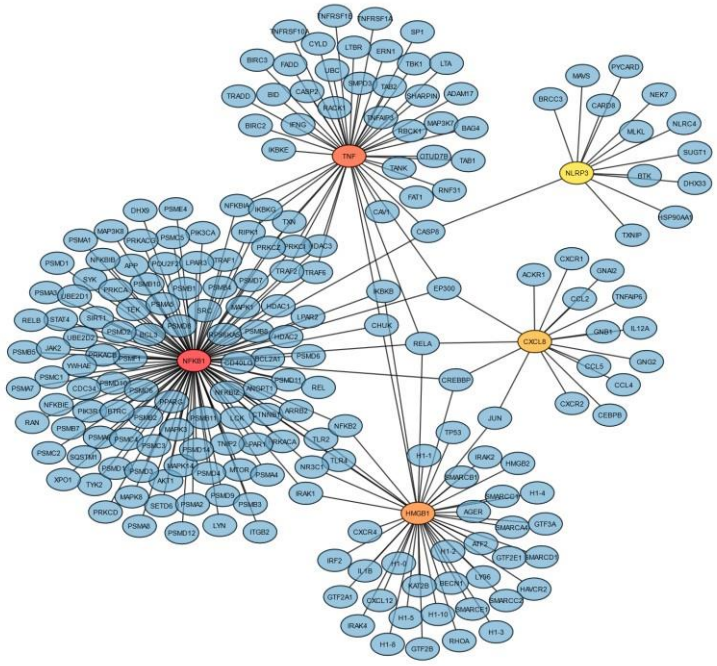
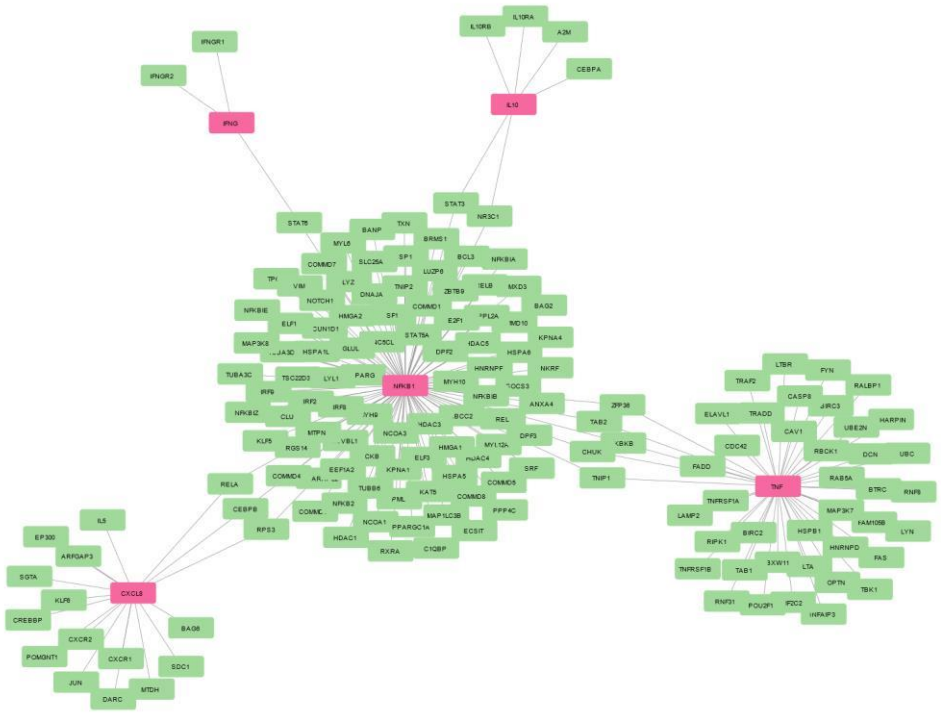
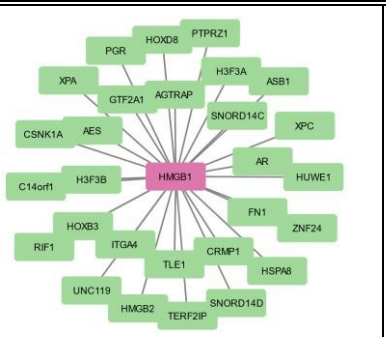


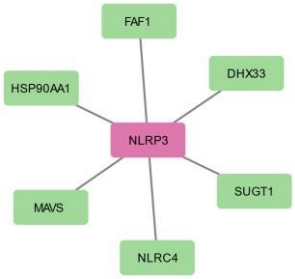
Figure 4. Identifying hub genes based on the generic PPI network between the nine common genes. The highlighted six genes (TNF, NFKB1, HMGB1, CXCL8, NLRP3). The hub genes were identified based o their degree value, where the degree value is > 10.



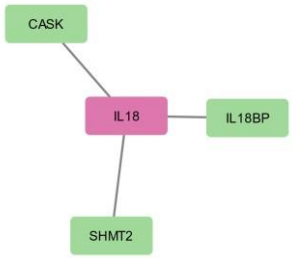
(a) Subnetwork1



(b) Subnetwork2



(c) Subnetwork3



(d) Subnetwork4

Figure 5. It represents the tissue-specific PPI network. Here the highlighted pink seed denotes the common genes, and the green color indicates the protein which is connected with the common genes.

3.3 Gene regulatory network (GRN).

Gene-miRNA interaction and TF-gene interaction network were analyzed for gene regulatory network. miRTarBase database has been used for the Gene-miRNA interaction network, and it creates one subnetwork. Figure 6 represents the Gene-miRNA interaction network with nine genes (HMGB1, NFKB1, IFNG, IL10, TNF, CXCL8, IL18, IL17A, and NLRP3) interacting with 229 miRNA. The gene is blue. hsa-mir-34a-5P, miRNA interconnect TNF, IL10, NFKB1, and HMGB1 genes. Figure 7 exhibits the TF-gene interaction network. The TF-gene interaction network analysis has been discovered in 2 subnetworks. Figure 7(a), subnetwork 1 has 54 TB, which is connected with the six genes (pink). NFKB1, IL10, NLRP3, IFNG, TNF, and HMGB1 are the genes of this network. Another subnetwork2, represent in Figure 7(b). It has 4 TF and one gene (pink). IL17A is the gene.

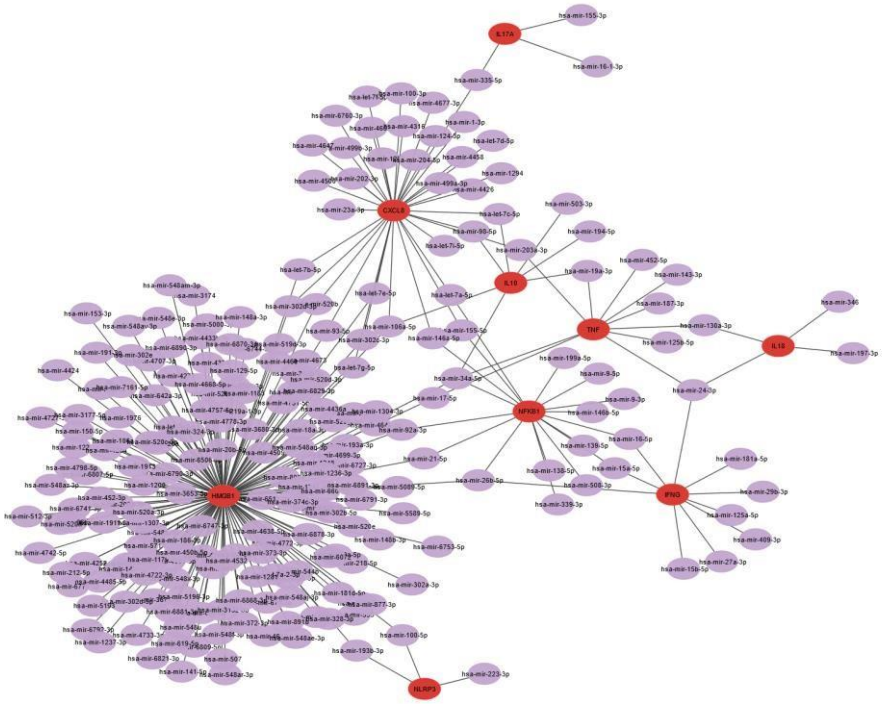
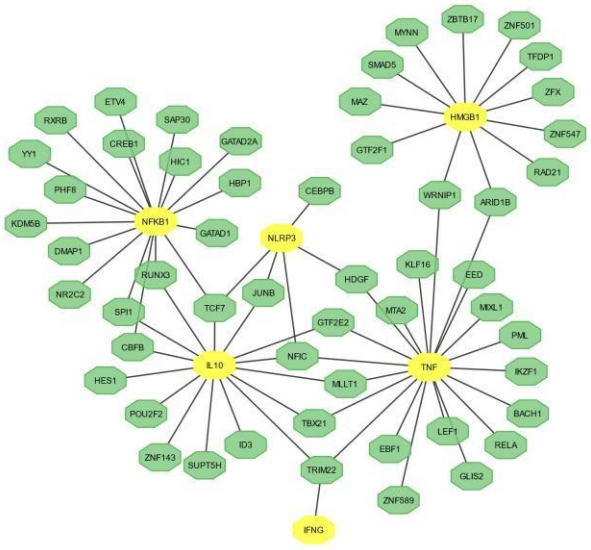
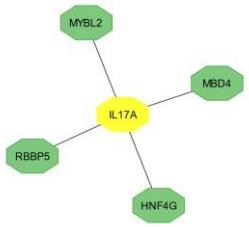


Figure 6. A network of Gene-miRNA interaction with common genes. The highlighted red node denotes common genes, while the remaining purple nodes are miRNA, which is connected with the genes.



(a) Subnetwork1

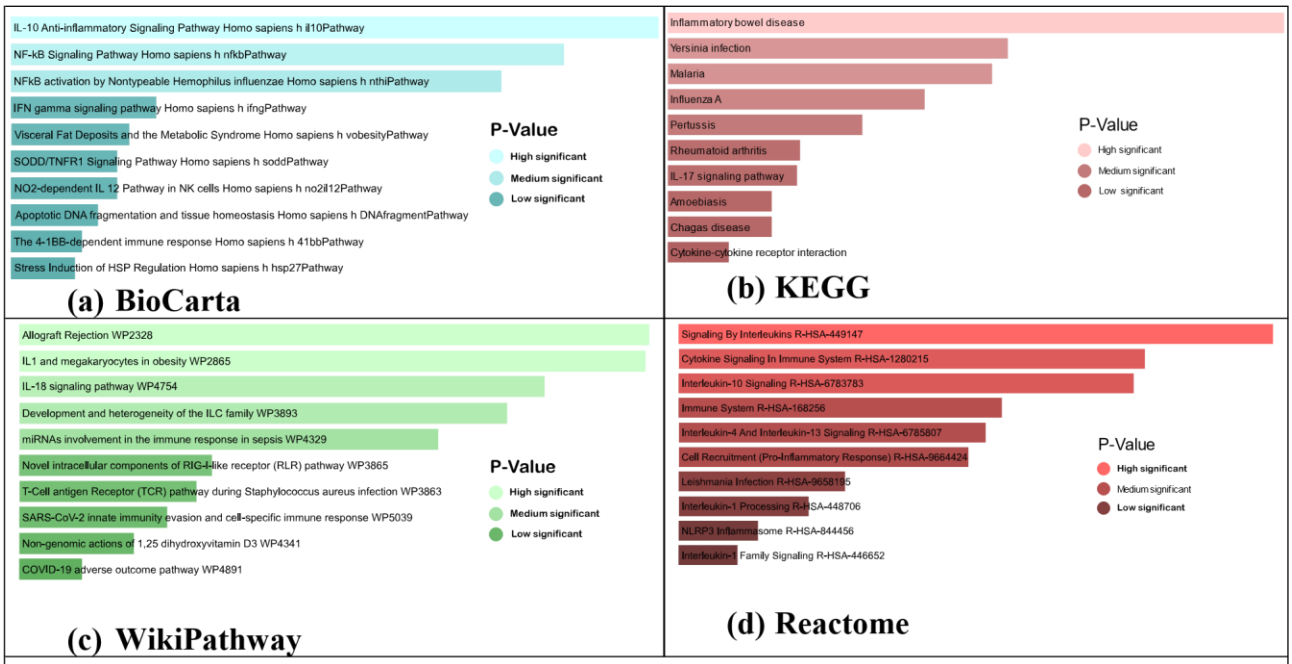


(a) Subnetwork2

Figure 7. A network of TF-gene interaction with common genes. The highlighted yellow node denotes common genes, while the remaining green nodes are TF which is connected with the genes.

3.4 Gene ontology and pathway enrichment analysis

After identifying the common genes, an enrichment analysis of the common gene was done to analyze the gene set using the Enrich. Several datasets were examined through to discover GO keywords and cellularly informative pathways. Table 4 displays Bio Carta, KEGG, WikiPathways, and Reactome pathway data. According to the KEGG pathway database- the Inflammatory bowel disease, Yersinia infection, Influenza A, Cytokine cytokine receptor interaction interact with the most genes. Table 4 displays the top 10 GO keywords for each category, as shown in the study. The number of gene interactions reveals underlying biological processes such as Positive regulation of cytokine production, Cellular response to lipopolysaccharide, Inflammatory response, Cytokine-mediated signaling pathway, etc. Cytokine activity, Receptor ligand activity, cytokine receptor binding, and other molecular functions are displayed in molecular functions. cytoplasmic vesicle lumen, secretory granule lumen, etc., are discovered in cellular components. Figures 8 and 10 lists GO keywords and pathways by p-value score. Figure 9 illustrates the functional enrichment analysis.



Figures 8(a), (b), (c), and (d) depict the analysis using BioCarta, KEGG, Reactome, and WikiPathway, based on the total P-value.

Table 3. Top pathways from the KEGG, Wikipathways, Bio Carta, and Reactome databases and their corresponding P-values and genes. Top pathways from the KEGG, Wikipathways, Bio Carta, and Reactome databases and their corresponding P-values and genes.

Database	Pathways	P values	Genes
Bio Carta	IL-10 Anti-inflammatory Signaling Pathway Homo sapiens h il10Pathway	1.40E-05	IL10, TNF
	NF-kB Signaling Pathway Homo sapiens h nfkbPathway	3.76E-05	TNF, NFKB1
	NFkB activation by No typeable Hemophilus influenzae Homo sapiens h nthiPathway	7.26E-05	CXCL8, TNF
	IFN gamma signaling pathway Homo sapiens h ifngPathway	0.002697	IFNG

	Visceral Fat Deposits and the Metabolic Syndrome Homo sapiens h vobesityPathway	0.003595	TNF
	SODD/TNFR1 Signaling Pathway Homo sapiens h soddPathway	0.004043	TNF
	NO2-dependent IL 12 Pathway in NK cells Homo sapiens h no2il12Pathway	0.004043	IFNG
	Apoptotic DNA fragmentation and tissue homeostasis Homo sapiens h DNAfragmentPathway	0.00494	HMGB1
	The 4-1BB-dependent immune response Homo sapiens h 41bbPathway	0.005836	IFNG
	Stress Induction of HSP Regulation Homo sapiens h hsp27Pathway	0.006284	TNF
KEGG	Inflammatory bowel disease	7.75E-14	IL10, IFNG, IL18, TNF, NFKB1, IL17A
	Yersinia infection	7.64E-12	IL10, CXCL8, IL18, NLRP3, TNF, NFKB1
	Malaria	9.94E-12	IL10, CXCL8, IFNG, IL18, TNF
	Influenza A	3.05E-11	CXCL8, IFNG, IL18, NLRP3, TNF, NFKB1
	Pertussis	8.63E-11	IL10, CXCL8, NLRP3, TNF, NFKB1
	Rheumatoid arthritis	2.42E-10	CXCL8, IFNG, IL18, TNF, IL17A
	IL-17 signaling pathway	2.56E-10	CXCL8, IFNG, TNF, NFKB1, IL17A

	Amoebiasis	3.87E-10	IL10, CXCL8, IFNG, TNF, NFKB1
	Chagas disease	3.87E-10	IL10, CXCL8, IFNG, TNF, NFKB1
	Cytokine-cytokine receptor interaction	7.92E-10	IL10, CXCL8, IFNG, IL18, TNF, IL17A
Wiki Pathway	Allograft Rejection WP2328	1.93E-10	IL10, CXCL8, IFNG, TNF, IL17A
	IL1 and megakaryocytes in obesity WP2865	2.00E-10	IFNG, IL18, NLRP3, NFKB1
	IL-18 signaling pathway WP4754	4.86E-10	IL10, CXCL8, IFNG, IL18, TNF, NFKB1
	Development and heterogeneity of the ILC family WP3893	6.76E-10	IFNG, IL18, TNF, IL17A
	miRNAs involvement in the immune response in sepsis WP4329	1.24E-09	IL10, CXCL8, TNF, NFKB1
	Novel intracellular components of RIG-I-like receptor (RLR) pathway WP3865	9.11E-09	CXCL8, IFNG, TNF, NFKB1
	T-Cell antigen Receptor (TCR) pathway during Staphylococcus aureus infection WP3863	1.04E-08	IL10, IFNG, TNF, NFKB1
	SARS-CoV-2 innate immunity evasion and cell-specific immune response WP5039	1.35E-08	IL10, CXCL8, TNF, NFKB1
	Non-genomic actions of 1,25 dihydroxy vitamin D3 WP4341	1.81E-08	CXCL8, IFNG, TNF, NFKB1

	COVID-19 adverse outcome pathway WP4891	2.86E-08	IL10, CXCL8, TNF
Reactome	Signaling by Interleukins R-HSA449147	1.01E-10	IL10, CXCL8, IFNG, IL18, HMGB1, TNF, NFKB1
	Cytokine Signaling in Immune System R-HSA-1280215	2.16E-09	IL10, CXCL8, IFNG, IL18, HMGB1, TNF, NFKB1
	Interleukin-10 Signaling R-HSA6783783	2.79E-09	IL10, CXCL8, IL18, TNF
	Immune System R-HSA-168256	6.44E-08	IL10, CXCL8, IFNG, IL18, NLRP3, HMGB1, TNF, NFKB1
	Interleukin-4 And Interleukin-13 Signaling R-HSA-6785807	9.56E-08	IL10, CXCL8, IL18, TNF
	Cell Recruitment (Pro-Inflammatory Response) R-HSA-9664424	1.44E-07	IL18, NLRP3, NFKB1
	Leishmania Infection R-HSA9658195	2.72E-06	IL10, IL18, NLRP3, NFKB1
	Interleukin-1 Processing R-HSA448706	6.47E-06	IL18, NFKB1
	NLRP3 Inflammasome R-HSA844456	2.15E-05	NLRP3, NFKB1
	Interleukin-1 Family Signaling R-HSA-446652	3.50E-05	IL18, HMGB1, NFKB1

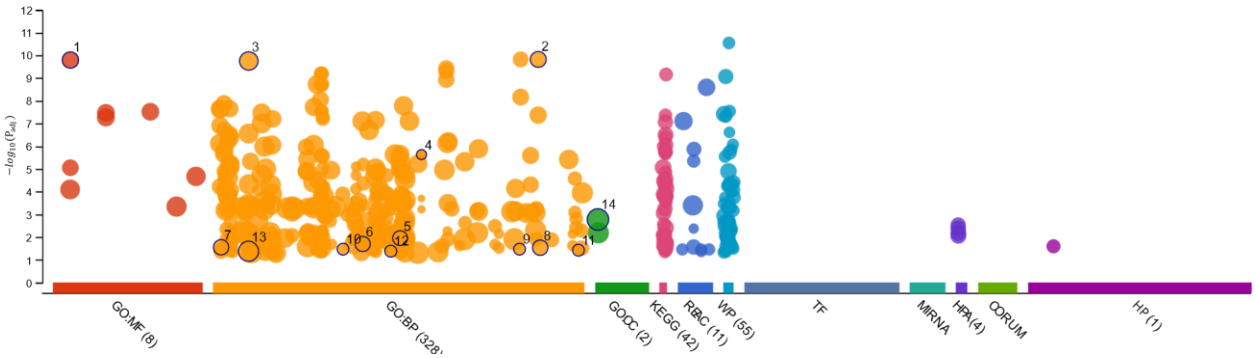


Figure 9. The analysis of functional enrichment of 9 common genes, Gene ontology, and pathways is displayed on a cluster plot based on log10(Pad) values on the Y axis.

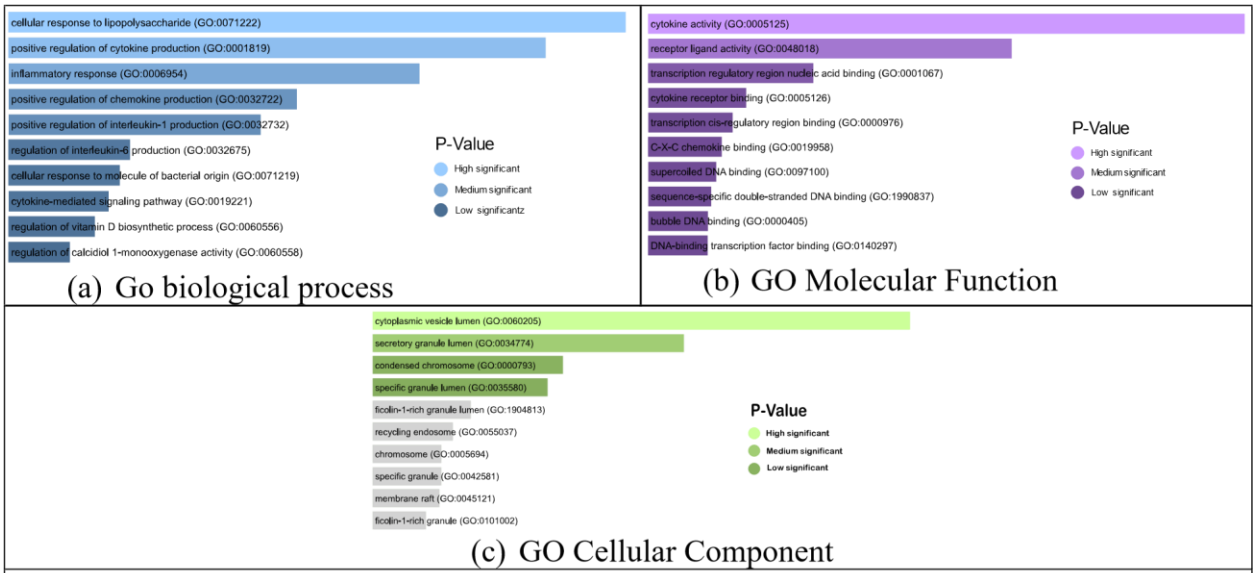


Figure 10 (a),(b), and (c) illustrate the biological process, molecular process, and cellular components, respectively, according to the combined score.

Table 4. GO terms, GO pathways, and their respective P-values, as well as genes for common genes

Category	GO ID	GO pathways	P-values	Genes
GO biological process	GO:0071222	Cellular response to lipopolysaccharide	8.35E-15	IL10, CXCL8, IL18, NLRP3, HMGB1, TNF, NFKB1
	GO:0001819	Positive regulation of cytokine production	5.06E-15	IL10, IFNG, IL18, NLRP3, HMGB1, TNF, NFKB1, IL17A
	GO:0006954	Inflammatory response	8.57E-13	CXCL8, IFNG, IL18, NLRP3, HMGB1, TNF, NFKB1
	GO:0032722	Positive regulation of chemokine production	1.35E-11	IFNG, IL18, HMGB1, TNF, IL17A
	GO:0032732	Positive regulation of interleukin-1 production	3.03E-11	IFNG, NLRP3, HMGB1, TNF, IL17A
	GO:0032675	Regulation of interleukin6 production	5.68E-10	IL10, IFNG, HMGB1, TNF, IL17A
	GO:0071219	Cellular response to molecule of bacterial origin	7.12E-10	IL10, CXCL8, NLRP3, HMGB1, NFKB1
	GO:0019221	Cytokine-mediated signaling pathway	9.18E-10	IL10, CXCL8, IFNG, IL18, TNF, NFKB1, IL17A
	GO:0060556	Regulation of vitamin D biosynthetic process	1.26E-09	IFNG, TNF, NFKB1
	GO:0060558	Regulation of calcitriol 1monooxygenase activity	2.20E-09	IFNG, TNF, NFKB1

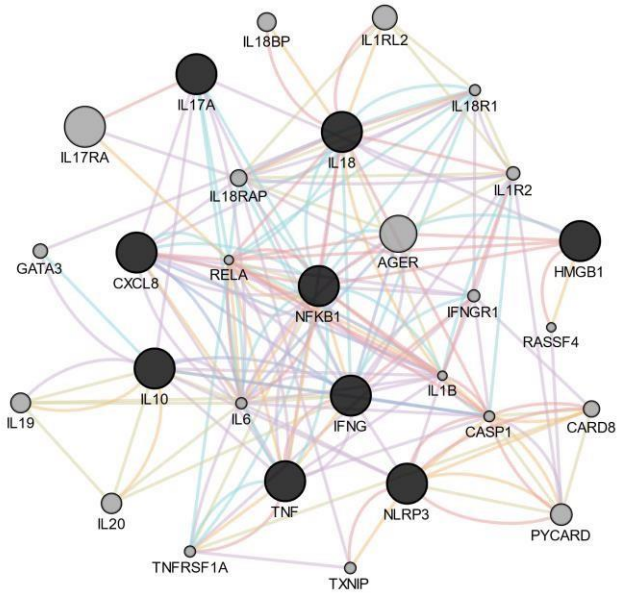
GO Molecular Function	GO:0005125	cytokine activity	3.16E-11	IL10, CXCL8, IFNG, IL18, HMGB1, TNF
	GO:0048018	receptor ligand activity	9.88E-08	IL10, IFNG, IL18, HMGB1, TNF
	GO:0001067	transcription regulatory region nucleic acid binding	9.41E-05	HMGB1, TNF, NFKB1
	GO:0005126	cytokine receptor binding	9.59E-04	IL10, IL18

	GO:0000976	transcription CIS regulatory region binding	0.00152706	HMGB1, TNF, NFKB1
	GO:0019958	C-X-C chemokine binding	0.002248161	HMGB1
	GO:0097100	supercoiled DNA binding	0.002697256	HMGB1
	GO:1990837	sequence-specific double stranded DNA binding	0.003213257	HMGB1, TNF, NFKB1
	GO:0000405	bubble DNA binding	0.003594909	HMGB1
	GO:0140297	DNA-binding transcription factor binding	0.003693126	NLRP3, HMGB1
GO Cellular Component	GO:0060205	cytoplasmic vesicle lumen	0.001149208	HMGB1, NFKB1
	GO:0034774	secretory granule lumen	0.008325128	HMGB1, NFKB1
	GO:0000793	condensed chromosome	0.024043797	HMGB1

	GO:0035580	specific granule lumen	0.027561797	NFKB1
	GO:1904813	ficolin-1-rich granule lumen	0.054018044	HMGB1
	GO:0055037	recycling endosome	0.063401467	TNF
	GO:0005694	chromosome	0.069751729	HMGB1
	GO:0042581	specific granule	0.069751729	NFKB1
	GO:0045121	membrane raft	0.071017179	TNF
	GO:0101002	ficolin-1-rich granule	0.079832569	HMGB1

3.5 Co-expression Network and Physical Interaction Network

Co-expression and Physical Interaction Networks have been done in the Cystoscope plugin- Gene MANIA (https://apps.cytoscape.org/apps/GeneMania). Figure 9 demonstrates the co-expression and physical interaction between related genes with 56.57% and 17.84%,



respectively. And co-localization was 6.18%, shared protein domains 1.00%, predicted 4.71%, and pathway 13.72% between the common genes.

Figure 11. Co-expression and Physical Interaction Network among the nine common genes. The red line denotes physical interaction. The purple line indicates co-expression, the green line defines genetic interaction, the blue line denotes co-localization, and the orange line denotes predicted.

Figure 12. illustrate the RNA expression patterns and protein co-regulation based on expression scores. For Homo sapiens CXCL8 and NFKB1 gene has 0.118, CXCL8 and IL18 has 0.088, CXCL8 and NLRP3 has 0.095, IL10 and TNF has 0.097, IL10 and NLRP3 has 0.090, IL17A and IFNG has 0.099, NFKB1 and TNF has 0.108, NFKB1 and NLRP3 has 0.071, TNF and NLRP3 has 0.146, TNF and IFNG has 0.152, IL18 and NLRP3 has 0.085, and NLRP3 and IFNG has 0.058 has RNA co-expression score. HMGB1 and NFKB1 has 0.042 base on protein coregulation.

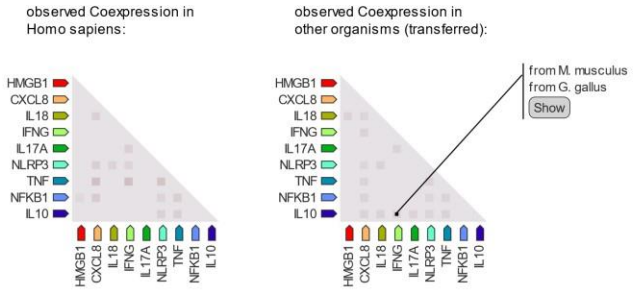


Figure 12. The heatmap shows the co-expression scores are based on RNA and proteins in Homo sapiens and other organisms.

3.6 Identify drug candidate.

Enrich, was used to suggest the therapeutic compounds from the DSigDB database. According to the nine-common gene (HMGB1, NFKB1, IFNG, IL10, TNF, CXCL8, IL17A, and NLRP3), the drug compounds were suggested. P-value and adjusted P-value both scores were used to get the results. bay 11-7082 CTD 00003959, PD 98059 CTD 00003206, and aspirin CTD 00005447 drugs are important drug compounds that are linked to a large number of genes. Besides, among the 5 hub genes, 4 hub genes (NFKB1, TNF, CXCL8, NLRP3, and IL10) were connected to the three drug compounds. This makes the drug compounds even more important for how well the drugs work. Table 4 shows the predictive drug compounds.

CHAPTER 6

DISCUSSION

The major objective of this research was to identify any genetic links that might exist between a variety of disorders. According to PTB and NCDs, common genes were identified between the gene datasets for establishing relationships and identifying potential drug candidates. 9 common genes (TNF, HMGB1, NFKB1, CXCL8, NLRP3, IL10, IFNG, IL18, and IL17A) were found. The study analyzes PPIs, GO, pathways, gene regulatory networks, candidate drug detection, co-expression, and physical interaction networks.

Nine common genes were utilized to construct generic PPI and tissue-specific PPI networks. PPI networks demonstrate proteomic information about PTB and NCDs. The generic PPI network identified five hub genes (CXCL8, NFKB1, TNF, IFNG, IL10) based on the degree value. The degree is normalized by the node number in the root set [59]. The tumor necrosis factor (TNF) gene has been linked to PTB and NCDs [60, 61]. The hub genes also revealed the presence of highly interconnected modules. IL-10 may help with the discovery of targeted therapies for neurodegenerative disease. IL10 reduces TNF-α production in PD and increases Brain-derived neurotrophic factor (BDNF) levels [62]. In tissue specific PPI, NFKB1 gene interact with highest number of proteins (subnetwork1).

The regulation of nine common genes is confirmed by analyzing the gene regulatory network based on the performance of TF genes and miRNAs. From GRN analysis, 229 miRNA and 54 TF (subnetwork1), and 4 TF (subnetwork2) were extracted from the nine genes. HMGB1 gene interconnects with the highest number of miRNAs with a 171-degree value. hsa-mir-34a-5P interact 4 genes (TNF, IL10, NFKB1, and HMGB1). TCF7, NFIC, and TRIM22 are the most interacted TF in the network. TF-genes serve as regulators for the gene expression that may cause the generation of cancer cells [63]. TNF and NFKB1 interacted with the highest amount of TF with 20- and 17-degree values respectively. NFKB1 is linked to the risk of getting cancer, and the link may be specific to a certain class [64]. Functional analysis discovered several common relationships that could be the reason for the higher death of NCDs patients after PTB. TCF7 TF contributes to pulmonary infection and assists in tissue regeneration and repair after severe lung damage [65].

Nine commonly used genes were utilized to identify GO terms and pathways. According to the P-values, GO terms and pathways were determined, where the P-value is <0.05. The results were statistically significant if the P-value was less than 0.05 [66]. cellular response to lipopolysaccharide, positive regulation of cytokine production, inflammatory response, cytokine-mediated signaling pathway, etc. are the top GO terms in biological processes. The inflammatory response is linked to the development of pulmonary tuberculosis. Inhibiting inflammatory responses may help ICU patients with PTB [67]. From molecular function, cytokine activity, receptor ligand activity, cytokine receptor binding, etc. GO terms were found. Cytokine genes have been identified in connection with increased cytokine levels, and they play a crucial role in active TB disease. IFNG, TNF, IL17A, and IL10 genes are all associated with various levels of cytokines in PTB patients and the development and maintenance of cellular immunity to TB, and the outcomes of active disease while on TB treatment [68]. Inflammatory bowel disease, Yersinia infection, malaria, influenza A, pertussis, rheumatoid arthritis, IL-17 signaling pathway, amoebiasis, Chagas disease, cytokine-cytokine receptor interaction were the top 10 pathways extracted from KEGG database to analysis pathways. IL-10 Anti-inflammatory Signaling Pathway Homo sapiens h il10Pathway, NF-kB Signaling Pathway Homo sapiens h nfkbPathway, NFkB activation by No typeable Hemophilus influenzae Homo sapiens h nthiPathway are highly connected with genes in Bio Carta. In the wikiPathwas pathway, IL-18 signaling pathway WP4754 is the highest-connected gene pathway. From the reactome pathway, signaling By Interleukins R-HSA-449147, cytokine Signaling in Immune System R-HSA-1280215, immune System R-HSA168256 were found with highly connected with genes. DSigDB database has been used to identify the drug component. The top 10 drug components- peritonitis, lupus nephritis, synovitis, Sjogren's syndrome, bacterial infections, celiac disease, cryopyrin-associated periodic syndromes, hepatitis, pneumonitis, inflammatory dermatosis were identified based on P-values and adjusted P-values.

Using Gene MANIA, co-expression, and physical interaction networks were explored. This analysis shows the correlation between the gene pair. The functional connection among genes in molecular networks has led to a new framework in which it is thought that common and rare diseases are caused by genomic and environmental factors that change whole molecular networks [69].

CHAPTER 7
CONCLUSION

This bioinformatics study examined at the connections, paths, and drug parts between Pulmonary Tuberculosis and NCDs like lung cancer, diabetes mellitus, Parkinson's disease, silicosis, chronic kidney disease, cardiovascular disease, and rheumatoid arthritis. Nine genes (NFKB1, IFNG, TNF, HMGB1, CXCL8, NLRP3, IL18, IL17A, and IL10) were linked to these diseases' development and spread. Gene ontology and pathway analysis were used to determine the biological processes and pathways these genes involved. The fact that these genes were found in many pathways linked to inflammatory response, immune response, and cytokine signaling suggests that they play a role in how these diseases start. Through more screening of a network of protein-protein interactions, five hub genes (NFKB1, TNF, CXCL8, NLRP3, and IL10) were found to be possible drug targets for further study. These genes were chosen because they have a lot of connections and are essential in the network. The results of this study give important information about possible drug targets that could be used to treat common diseases. This study has implications for bio informaticists, doctors, the search for new drugs, and other complex fields of study. In vitro and in vivo studies could be used to confirm these possible drug targets. In the long run, better patient outcomes may be achieved by the discovery of innovative medications that target these genes for the treatment of these prevalent diseases.

REFERENCE

1. GBD Tuberculosis Collaborators. The global burden of tuberculosis: results from the Global Burden of Disease Study 2015. Lancet Infect Dis. 2018 Mar;18(3):261284. doi: 10.1016/S1473-3099(17)30703-X. Epub 2017 Dec 7. PMID: 29223583; PMCID: PMC5831985.

2. Garrido-Cardenas, J.A.; de Lamo-Sevilla, C.; Cabezas-FernÃ¡ndez, M.T.; Manzano-Agugliaro, F.; MartÃ-nez-Lirola, M. (2020). Global tuberculosis research and its future prospects. Tuberculosis, (), 101917–. doi:10.1016/j.tube.2020.101917
3. Jeremiah Chakaya;Mishal Khan;Francine Ntoumi;Eleni Aklillu;Razia Fatima;Peter Mwaba;Nathan Kapata;Sayoki Mfinanga;Seyed Ehtesham Hasnain;Patrick D.M.C. Katoto;André N.H. Bulabula;Nadia A. Sam-Agudu;Jean B. Nachega;Simon Tiberi;Timothy D. McHugh;Ibrahim Abubakar;Alimuddin Zumla; (2021). Global Tuberculosis Report 2020 – Reflections on the Global TB burden, treatment and prevention efforts . International Journal of Infectious Diseases, (), –. doi:10.1016/j.ijid.2021.02.107
4. Feleke, B.E., Feleke, T.E. & Biadglegne, F. Nutritional status of tuberculosis patients, a comparative cross-sectional study. BMC Pulm Med 19, 182 (2019). https://doi.org/10.1186/s12890-019-0953-0
5. Wang, Y., Wang, J. Modelling and prediction of global non-communicable diseases. BMC Public Health 20, 822 (2020). https://doi.org/10.1186/s12889-02008890-4
6. Stubbs, B.; Siddiqi, K.; Elsey, H.; Siddiqi, N.; Ma, R.; Romano, E.; Siddiqi, S.; Koyanagi, A. Tuberculosis and Non-Communicable Disease Multimorbidity: An Analysis of the World Health Survey in 48 Low- and Middle-Income Countries. Int. J. Environ. Res. Public Health 2021, 18, 2439. https://doi.org/10.3390/ijerph18052439
7. Allen LN, Wigley S, Holmer H. Implementation of non-communicable disease policies from 2015 to 2020: a geopolitical analysis of 194 countries. Lancet Glob Health. 2021 Nov;9(11):e1528-e1538. doi: 10.1016/S2214-109X(21)00359-4. Erratum in: Lancet Glob Health. 2021 Nov 10;: PMID: 34678197.
8. Sharma, Parvarish; Mehta, Meenu; Dhanjal, Daljeet Singh; Kaur, Simran; Gupta, Gaurav; Singh, Harjeet; Thangavelu, Lakshmi; Kumar, S. Rajesh; Tambuwala, Murtaza; Bakshi, Hamid A.; Chellappan, Dinesh Kumar; Dua, Kamal; Satija, Saurabh (2019). Emerging trends in the novel drug delivery approaches for the treatment of lung cancer. Chemico-Biological Interactions, (), S0009279719307653–. doi:10.1016/j.cbi.2019.06.033

9. Woodman, Christopher; Vundu, Gugulethu; George, Alex; Wilson, Cornelia M. (2020). Applications and strategies in nanodiagnosis and nanotherapy in lung cancer. Seminars in Cancer Biology, (), S1044579X20300420–. doi:10.1016/j.semcancer.2020.02.009
10. Shobana Sundar;Lokesh Thangamani;Shanmughavel Piramanayagam;Jeyakumar Natarajan; (2021). Screening of Mycobacterium tuberculosis genes as putative drug targets for treatment of HIV-TB and lung cancer-TB comorbidities: An in silico analysis . Gene Reports, (), –. doi:10.1016/j.genrep.2021.101215
11. Massimiliano Lanzafame;Sandro Vento; (2021). Mini-review: Silico-tuberculosis . Journal of Clinical Tuberculosis and Other Mycobacterial Diseases, (), –. doi:10.1016/j.jctube.2021.100218
12. Salahuddin, M., Cawasji, Z., Kaur, S. et al. Current Concepts in Pathogenesis, Diagnosis, and Management of Silicosis and Its Subtypes. Curr Pulmonol Rep 10, 135–142 (2021). https://doi.org/10.1007/s13665-021-00279-x
13. Ng, Jack K-C; Li, Philip K-T (2018). Chronic kidney disease epidemic: How do we deal with it?. Nephrology, 23(), 116–120. doi:10.1111/nep.13464
14. Campbell, Jonathon R.; Johnston, James C.; Ronald, Lisa A.; Sadatsafavi, Mohsen; Balshaw, Robert F.; Cook, Victoria J.; Levin, Adeera; Marra, Fawziah (2018). Screening for Latent Tuberculosis Infection in Migrants With CKD: A Costeffectiveness Analysis. American Journal of Kidney Diseases, (), S0272638618308783–. doi:10.1053/j.ajkd.2018.07.014
15. Cahuayme-Zuniga, Lizbeth J.; Brust, Karen B. (2019). Mycobacterial Infections in Patients With Chronic Kidney Disease and Kidney Transplantation. Advances in Chronic Kidney Disease, 26(1), 35–40. doi:10.1053/j.ackd.2018.09.004
16. Bullock, Jacqueline; Rizvi, Syed A.A.; Saleh, Ayman M.; Ahmed, Sultan S.; Do, Duc P.; Ansari, Rais A.; Ahmed, Jasmin (2018). Rheumatoid Arthritis: A Brief Overview of the Treatment. Medical Principles and Practice, (), –. doi:10.1159/000493390
17. van Delft, Myrthe AM, and Tom WJ Huizinga. "An overview of autoantibodies in rheumatoid arthritis." Journal of autoimmunity 110 (2020): 102392.
18. Sophia M. Naz; Deborah P.M. Symmons (2007). Mortality in established rheumatoid arthritis. , 21(5), 871–883. doi:10.1016/j.berh.2007.05.003
19. Abásolo L, Júdez E, Descalzo MA, González-Alvaro I, Jover JA, Carmona L; EMECAR Study Group. Cancer in rheumatoid arthritis: occurrence, mortality, and associated factors in a South European population. Semin Arthritis Rheum. 2008 Jun;37(6):388-97. doi: 10.1016/j.semarthrit.2007.08.006. Epub 2007 Oct 30. PMID: 17977580.
20. Hayes, M.T. (2019). Gender Differences in Parkinson's Disease. In: O'Neal, M. (eds) Neurology and Psychiatry of Women. Springer, Cham. https://doi.org/10.1007/978-3-030-04245-5_24
21. H. Zhang, C. Song, A. S. Rathore, M. -C. Huang, Y. Zhang and W. Xu, "mHealth Technologies Towards Parkinson's Disease Detection and Monitoring in Daily

Life: A Comprehensive Review," in IEEE Reviews in Biomedical Engineering, vol. 14, pp. 71-81, 2021, doi: 10.1109/RBME.2020.2991813.
22. Dhingra, Ravi; Vasan, Ramachandran S. (2016). Biomarkers in cardiovascular disease: Statistical assessment and section on key novel heart failure biomarkers. Trends in Cardiovascular Medicine, (), S1050173816301050–. doi:10.1016/j.tcm.2016.07.005.
23. Ormazabal, V., Nair, S., Elfeky, O. et al. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 17, 122 (2018). https://doi.org/10.1186/s12933-018-0762-4
24. Pinheiro, L.C., Reshetnyak, E., Sterling, M.R. et al. Using health-related quality of life to predict cardiovascular disease events. Qual Life Res 28, 1465–1475 (2019). https://doi.org/10.1007/s11136-019-02103-1
25. Suryasa, I. W., Rodríguez-Gámez, M., & Koldoris, T. (2021). Health and treatment of diabetes mellitus. International Journal of Health Sciences, 5(1), i-v. https://doi.org/10.53730/ijhs.v5n1.2864
26. Ho, James Chung-man; Leung, Chi-Chiu (2018). Management of co-existent tuberculosis and lung cancer. Lung Cancer, 122(), 83–87. doi:10.1016/j.lungcan.2018.05.030
27. Abd-El-Fattah, A.A., Sadik, N.A.H., Shaker, O.G. et al. Differential MicroRNAs Expression in Serum of Patients with Lung Cancer, Pulmonary Tuberculosis, and Pneumonia. Cell Biochem Biophys 67, 875–884 (2013). https://doi.org/10.1007/s12013-013-9575-y
28. Shu, CC., Wei, YF., Yeh, YC. et al. The impact on incident tuberculosis by kidney function impairment status: analysis of severity relationship. Respir Res 21, 51 (2020). https://doi.org/10.1186/s12931-020-1294-5
29. Chang, CH., Chen, YF., Wu, VC. et al. Acute kidney injury due to anti-tuberculosis drugs: a five-year experience in an aging population. BMC Infect Dis 14, 23 (2014). https://doi.org/10.1186/1471-2334-14-23
30. Leung, C.Y., Huang, HL., Rahman, M.M. et al. Cancer incidence attributable to tuberculosis in 2015: global, regional, and national estimates. BMC Cancer 20, 412 (2020). https://doi.org/10.1186/s12885-020-06891-5
31. Hasin Rehana;Md Raihan Ahmed;Rana Chakma;Sayed Asaduzzaman;M. Raihan; (2021). A bioinformatics approach for identification of the core ontologies and signature genes of pulmonary disease and associated disease . Gene Reports, (), –. doi:10.1016/j.genrep.2021.101206
32. Cheng, Matthew P.; Abou Chakra, Claire Nour; Yansouni, Cedric P; Cnossen, Sonya; Shrier, Ian; Menzies, Dick; Greenaway, Christina (2016). Risk of Active Tuberculosis in Patients with Cancer: A Systematic Review and Meta-Analysis. Clinical Infectious Diseases, (), ciw838–. doi:10.1093/cid/ciw838
33. Liao, Kuang-Ming, et al. "Prior Treated Tuberculosis and Mortality Risk in Lung Cancer." Frontiers in Medicine 10: 510.

34. Islam, M.R., Ahmed, M.L., Kumar Paul, B., Asaduzzaman, S., Ahmed, K. (2019). Common Gene Regulatory Network for Anxiety Disorder Using Cytoscape: Detection and Analysis. In: Rojas, I., Valenzuela, O., Rojas, F., Ortuño, F. (eds) Bioinformatics and Biomedical Engineering. IWBBIO 2019. Lecture Notes in Computer Science(), vol 11466. Springer, Cham. https://doi.org/10.1007/978-3030-17935-9_20
35. Chung, T.T., Ko, H.J., Lau, C.S. et al. A retrospective study on the risk of tuberculosis in patients with rheumatoid arthritis. Rheumatol Int 40, 983–990 (2020). https://doi.org/10.1007/s00296-020-04583-8
36. Ugarte-Gil, Cesar; Carrillo-Larco, Rodrigo M.; Kirwan, Daniela E. (2019). Latent tuberculosis infection and non-infectious co-morbidities: Diabetes mellitus type 2, chronic kidney disease and rheumatoid arthritis. International Journal of Infectious Diseases, (), S1201971219300827–. doi:10.1016/j.ijid.2019.02.018
37. Meng, L., Shen, L. & Ji, HF. Impact of infection on risk of Parkinson's disease: a quantitative assessment of case-control and cohort studies. J. Neurovirol. 25, 221–228 (2019). https://doi.org/10.1007/s13365-018-0707-4
38. Biosa, A., Outeiro, T.F., Bubacco, L. et al. Diabetes Mellitus as a Risk Factor for Parkinson's Disease: a Molecular Point of View. Mol Neurobiol 55, 8754–8763 (2018). https://doi.org/10.1007/s12035-018-1025-9
39. Glovaci, D., Fan, W. & Wong, N.D. Epidemiology of Diabetes Mellitus and Cardiovascular Disease. Curr Cardiol Rep 21, 21 (2019). https://doi.org/10.1007/s11886-019-1107-y
40. Potashkin J, Huang X, Becker C, Chen H, Foltynie T, Marras C. Understanding the links between cardiovascular disease and Parkinson's disease. Mov Disord. 2020 Jan;35(1):55-74. doi: 10.1002/mds.27836. Epub 2019 Sep 4. PMID: 31483535; PMCID: PMC6981000.
41. Sayers, Eric W; Agarwala, Richa; Bolton, Evan E; Brister, J Rodney; Canese, Kathi; Clark, Karen; Connor, Ryan; Fiorini, Nicolas; Funk, Kathryn; Hefferon, Timothy; Holmes, J Bradley; Kim, Sunghwan; Kimchi, Avi; Kitts, Paul A; Lathrop, Stacy; Lu, Zhiyong; Madden, Thomas L; Marchler-Bauer, Aron; Phan, Lon; Schneider, Valerie A; Schoch, Conrad L; Pruitt, Kim D; Ostell, James (2018). Database resources of the National Center for Biotechnology Information. Nucleic Acids Research, (), –. doi:10.1093/nar/gky1069
42. Guangyan Zhou, Othman Soufan, Jessica Ewald, Robert E W Hancock, Niladri Basu, Jianguo Xia, NetworkAnalyst 3.0: a visual analytics platform for comprehensive gene expression profiling and meta-analysis, Nucleic Acids Research, Volume 47, Issue W1, 02 July 2019, Pages W234–W241, https://doi.org/10.1093/nar/gkz240
43. Tanja Kortemme; David Baker (2004). Computational design of protein–protein interactions. , 8(1), 91–97. doi:10.1016/j.cbpa.2003.12.008

44. Damian Szklarczyk, Rebecca Kirsch, Mikaela Koutrouli, Katerina Nastou, Farrokh Mehryary, Radja Hachilif, Annika L Gable, Tao Fang, Nadezhda T Doncheva, Sampo Pyysalo, Peer Bork, Lars J Jensen, Christian von Mering, The STRING database in 2023: protein–protein association networks and functional enrichment analyses for any sequenced genome of interest, Nucleic Acids Research, Volume 51, Issue D1, 6 January 2023, Pages D638–D646, https://doi.org/10.1093/nar/gkac1000
45. von Mering C, Jensen LJ, Snel B, Hooper SD, Krupp M, Foglierini M, Jouffre N, Huynen MA, Bork P. STRING: known and predicted protein-protein associations, integrated and transferred across organisms. Nucleic Acids Res. 2005 Jan 1;33(Database issue):D433-7. doi: 10.1093/nar/gki005. PMID: 15608232; PMCID: PMC539959.
46. Basha O, Shpringer R, Argov CM, Yeger-Lotem E. The DifferentialNet database of differential protein-protein interactions in human tissues. Nucleic Acids Res. 2018 Jan 4;46(D1):D522-D526. doi: 10.1093/nar/gkx981. PMID: 29069447; PMCID: PMC5753382.
47. Su G, Morris JH, Demchak B, Bader GD. Biological network exploration with Cytoscape 3. Curr Protoc Bioinformatics. 2014 Sep 8;47:8.13.1-24. doi: 10.1002/0471250953.bi0813s47. PMID: 25199793; PMCID: PMC4174321.
48. Chin, CH., Chen, SH., Wu, HH. et al. cytoHubba: identifying hub objects and subnetworks from complex interactome. BMC Syst Biol 8 (Suppl 4), S11 (2014). https://doi.org/10.1186/1752-0509-8-S4-S11
49. Sonawane, Abhijeet Rajendra; Platig, John; Fagny, Maud; Chen, Cho-Yi; Paulson, Joseph Nathaniel; Lopes-Ramos, Camila Miranda; DeMeo, Dawn Lisa; Quackenbush, John; Glass, Kimberly; Kuijjer, Marieke Lydia (2017). Understanding Tissue-Specific Gene Regulation. Cell Reports, 21(4), 1077–1088. doi:10.1016/j.celrep.2017.10.001
50. Cozzolino M, Mangano M, Stucchi A, Ciceri P, Conte F, Galassi A. Cardiovascular disease in dialysis patients. Nephrol Dial Transplant. 2018 Oct 1;33(suppl_3):iii28iii34. doi: 10.1093/ndt/gfy174. PMID: 30281132; PMCID: PMC6168816.
51. Subramanian A, Kuehn H, Gould J, Tamayo P, Mesirov JP. GSEA-P: a desktop application for Gene Set Enrichment Analysis. Bioinformatics. 2007 Dec 1;23(23):3251-3. doi: 10.1093/bioinformatics/btm369. Epub 2007 Jul 20. PMID: 17644558.
52. Harris MA, Clark J, Ireland A, Lomax J, Ashburner M, Foulger R, Eilbeck K, Lewis S, Marshall B, Mungall C, Richter J, Rubin GM, Blake JA, Bult C, Dolan M, Drabkin H, Eppig JT, Hill DP, Ni L, Ringwald M, Balakrishnan R, Cherry JM, Christie KR, Costanzo MC, Dwight SS, Engel S, Fisk DG, Hirschman JE, Hong EL, Nash RS, Sethuraman A, Theesfeld CL, Botstein D, Dolinski K, Feierbach B, Berardini T, Mundodi S, Rhee SY, Apweiler R, Barrell D, Camon E, Dimmer E,