THE ANATOLIAN JOURNAL OF CARDIOLOGY

Official journal of the TURKISH SOCIETY OF CARDIOLOGY

Selection of Common Genes Associated with Rheumatoid Arthritis and Cardiovascular Disease via a Network- and Pathway-Based Approach

ABSTRACT

Background: Patients with rheumatoid arthritis (RA) have an increased risk of developing cardiovascular disease (CVD). However, the mechanisms underlying the comorbidity between RA and CVD remain poorly understood. This study aimed to identify the shared genes between RA and CVD and to explore their functional relationships.

Methods: Rheumatoid arthritis– and CVD-associated genes were obtained from the DisGeNET and Malacards databases, respectively. Shared genes between the 2 diseases were identified, and gene ontology and Kyoto Encyclopedia of Genes and Genomes pathway enrichment analyses were performed using WebGestalt and Cytoscape (v3.9.0). To further investigate potential molecular interactions, protein–protein interaction networks were constructed based on data from the STRING database. Finally, the in silico Tabula Muris single-cell transcriptomic dataset was used to assess the tissue-specific expression of candidate genes and evaluate their potential roles in specific tissues and cell types.

Results: A total of 108 genes were shared between RA and CVD, out of the 898 and 552 genes identified for each condition. Functional enrichment analysis showed that these shared genes were predominantly associated with inflammation and immune response–related pathways. Among them, 42 candidate genes were identified, of which 7 (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1,* and *CD44*) were highlighted based on their strong connectivity and biological relevance. For validation, the validation, Tabula Muris single-cell transcriptomic dataset revealed that these genes were highly expressed in mouse cardiac tissues.

Conclusion: Seven shared genes associated with both RA and CVD were identified, which may contribute to the comorbidity between the 2 diseases.

Keywords: Cardiovascular disease, enrichment analysis, immune response, rheumatoid arthritis, shared genes

INTRODUCTION

Rheumatoid arthritis (RA) and cardiovascular disease (CVD) have overlapping pathophysiologic mechanisms involving inflammation, immunity, and oxidative stress.[1,2] Rheumatic diseases have been considered vital in the interplay between heart disease and inflammation.[3] In the preclinical stage of RA, the self-tolerance of the immune system is decreased, and various autoantibodies are produced.[4] This subsequently activates the immune system and ultimately leads to immune infiltration into the joint synovium. It is a complex process involving a large number of cytokines and pro-inflammatory cytokines, such as tumor necrosis factor-alpha and interleukin-1 (IL-1), which can stimulate the generation of reactive oxygen species and consequently lead to oxidative stress and cellular injury.[5,6]

Although there is definite evidence for the shared mechanisms of RA and CVD, there is still a lack of studies at the molecular level. To date, the understanding of the genes associated with RA and CVD is still limited due to lacking of appropriate techniques and approaches. The increasing availability of large-scale genomic data, such as UK Biobank data, facilitates the investigation of CVD risk-related pathways among RA patients at the molecular level.[7] Notably, recent Mendelian

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ORIGINAL INVESTIGATION

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Received: March 31, 2025
Accepted: July 23, 2025
Available Online Date: September 15, 2025

Cite this article as: Bai YB, Bai YP, Wu Z, Chen Q, Jiang N. Selection of common genes associated with rheumatoid arthritis and cardiovascular disease via a network- and pathway-based approach. *Anatol J Cardiol.* 2025;29(12):701-714.

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DOI:10.14744/AnatolJCardiol.2025.5375

randomization (MR) studies have provided new insights into the causal relationships between RA and CVD.[8,9] For example, Qiu et al[8] performed an MR analysis and reported that RA was potentially causally associated with 6 types of cardiovascular conditions, including age-related angina pectoris, hypertension, age-related heart attack, abnormal heart rate, stroke, and general heart disease. Similarly, Wang et al[9] identified a causal relationship between RA and ischemic heart disease, as well as myocardial infarction (MI). Their study further suggested that reducing RA disease activity could potentially lower CVD risk. Based on the genome-wide data, Guo et al[10] performed a conventional meta-analysis to assess the shared genetic architecture between RA and CVD using the UK Biobank. Their results supported the idea that there is shared genetic pathogenesis in explaining the observed association between RA and CVD.

To further investigate the molecular association between CVD and RA, disease-associated genes were systematically collected from the MalaCards and DisGeNET databases. Subsequently, functional enrichment analysis was conducted to identify the key biological processes and signaling pathways enriched in the shared genes, as well as their potential interactions. Finally, the potential hub genes were identified based on their central roles in the protein–protein interaction (PPI) network, which may be involved in the comorbidity of CVD and RA.

METHODS

Selection of Rheumatoid Arthritis– and Cardiovascular Disease–Associated Genes from Databases

A flowchart of the study design is shown in Supplementary Figure 1. Rheumatoid arthritis– and CVD-associated genes were extracted from DisGeNET (https://www.disgenet.org/) and Malacards (https://www.malacards.org/).[11,12] Genes with a gene-disease association score > 0.05 were selected from the DisGeNET database, as this threshold indicates a strong disease association. Additionally, the selection of associated genes from Malacards was performed based on default parameters as described in the previous study.[12] After retrieving RA- and CVD-associated genes from each database, the shared genes between the 2 diseases were identified. These shared genes were considered as potential susceptibility genes contributing to the comorbidity of RA and CVD and were used for enrichment and network analyses.

Functional and Pathway Enrichment Analyses

To explore the biological significance of the shared genes between RA and CVD, a series of functional annotation and pathway enrichment analyses were performed. Firstly, GO analysis was conducted using WebGestalt (http://www.webgestalt.org), with a focus on biological processes significantly enriched among the shared genes [False discovery rate (FDR) < 0.05].[13] To assess interactions at the protein level, a PPI network was constructed using Metascape (http://metascape.org/), and subnetworks were identified using the molecular complex detection algorithm.[14,15]

Hub gene selection was performed using ClueGO, CluePledia and CytoHubba.[16,17] Pathway enrichment analysis was conducted with ClueGO and CluePledia, followed by the identification of key hub genes in the PPI network using the Maximal Clique Centrality algorithm in CytoHubba.

To further investigate functional relationships among biological pathways, a pathway cross-talk analysis was conducted. Enriched KEGG pathways ($P < 0.05$) were identified using ToppGene (https://toppgene.cchmc.org/enrichment.jsp, FDR < 0.05) based on RA- and CVD-associated genes. Cross-talk between pathways was quantified using the Jaccard Coefficient ($A \cap B / A \cup B$) and Overlap Coefficient ($|A \cap B| / \min(|A|, |B|)$) to assess gene overlap between pathway pairs, where A and B represent the sets of genes in 2 pathways.[18-20] The pathway interaction network was visualized using Cytoscape (version 3.9.0), providing insight into functionally connected pathways potentially contributing to RA–CVD comorbidity.

Identification of Candidate Genes Through Protein–Protein Interaction Network Analysis

We first mapped the RA-associated genes and CVD-associated genes into the PPI network, which yielded an RA-specific network and a CVD-specific network, respectively. To exclude the irrelevant interactions, the RA-specific network and CVD-specific network were merged into a combined network. Subsequently, the RA-specific network was compared with the CVD-specific network, followed by the extraction of the overlapping network. The Cytoscape software was utilized to calculate the node degree of the genes using the Network Analyzer.[21,22] Then nodes with a degree of 5 or more were selected as candidate genes after removing the RA-associated and CVD-associated genes. For validation, the specific PPI network was also obtained from the STRING database and merged a combined network.

Expression Analysis of Candidate Genes from databases

To explore the tissue and cell-type-specific expression patterns of the candidate genes, an in silico expression analysis was performed using the Tabula Muris database (https://tabula-muris.ds.czbiohub.org/). The Tabula Muris Senis (TMS) dataset is a large-scale, publicly available single-cell RNA-seq dataset of mice. All cells in the dataset have been annotated with cell types by the TMS project. Log-transformed, pre-processed data was obtained from the TMS dataset, which comprises 2 subsets generated using distinct experimental methodologies: fluorescence-activated cell sorting (FACS) and droplet-based sequencing. Using FACS methods, the expression of predicted genes was analyzed in various tissues, including heart tissue, and in different cells.

HIGHLIGHTS

- To screen the rheumatoid arthritis (RA)– and cardiovascular disease (CVD)–associated genes, with the aim to investigate their comorbidity.
- Seven shared RA- and CVD-associated genes were responsible for the comorbidity of CVD and RA.
- Inflammation and immune responses were enriched in the shared genes.

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
LPA	4018	lipoprotein(a)	P08519
NOS3	4846	nitric oxide synthase 3	P29474
PON1	5444	paraoxonase 1	P27169
VCAM1	7412	vascular cell adhesion molecule 1	P19320
ICAM1	3383	intercellular adhesion molecule 1	P05362
CRP	1401	C-reactive protein	P02741
HP	3240	haptoglobin	P00738
MPO	4353	myeloperoxidase	P05164
CCL2	6347	C-C motif chemokine ligand 2	P13500
ALB	213	albumin	P02768
ACE	1636	angiotensin I converting enzyme	P12821
PTGS2	5743	prostaglandin-endoperoxide synthase 2	P35354
MTHFR	4524	methylenetetrahydrofolate reductase	P42898
SELE	6401	selectin E	P16581
GRK2	156	G protein-coupled receptor kinase 2	P25098
AGER	177	advanced glycosylation end-product specific receptor	Q15109
FTO	79068	FTO alpha-ketoglutarate dependent dioxygenase	Q9C0B1
VDR	7421	vitamin D receptor	P11473
COL4A1	1282	collagen type 4 alpha 1 chain	P02462
BANK1	55024	B cell scaffold protein with ankyrin repeats 1	Q8NDB2
MBL2	4153	mannose binding lectin 2	P11226
MIR21	406991	microRNA 21	nan
RETN	56729	resistin	Q9HD89
PLG	5340	plasminogen	P00747
MMP2	4313	matrix metallopeptidase 2	P08253
PIK3CG	5294	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma	P48736
SERPINE1	5054	serpin family E member 1	P05121
PLA2G2A	5320	phospholipase A2 group IIA	P14555
MMP9	4318	matrix metallopeptidase 9	P14780
PPARG	5468	peroxisome proliferator activated receptor gamma	P37231
CCHCR1	54535	coiled-coil alpha-helical rod protein 1	Q8TD31
NFE2L2	4780	nuclear factor, erythroid 2 like 2	Q16236
NFKBIA	4792	NFKB inhibitor alpha	P25963
TNFRSF11B	4982	TNF receptor superfamily member 11b	O00300
ADIPOQ	9370	adiponectin, C1Q and collagen domain containing	Q15848
CD36	948	CD36 molecule	P16671
CD14	929	CD14 molecule	P08571
TGFB1	7040	transforming growth factor beta 1	P01137
SAA1	6288	serum amyloid A1	P0DJI8
PRDM16	63976	PR/SET domain 16	Q9HAZ2
LINC00452	643365	long intergenic non-protein coding RNA 452	
BDNF	627	brain derived neurotrophic factor	P23560
PTX3	5806	pentraxin 3	P26022
VEGFA	7422	vascular endothelial growth factor A	P15692
SPP1	6696	secreted phosphoprotein 1	P10451
TLR4	7099	toll-like receptor 4	O00206
TNF	7124	tumor necrosis factor	P01375
DPP4	1803	dipeptidyl peptidase 4	P27487
ESR1	2099	estrogen receptor 1	P03372

(*Continued*)

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis (*Continued*)

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
ESR2	2100	estrogen receptor 2	Q92731
F2	2147	coagulation factor II, thrombin	P00734
CHI3L1	1116	chitinase 3 like 1	P36222
NLRP3	114548	NLR family pyrin domain containing 3	Q96P20
ADM	133	adrenomedullin	P35318
NR3C1	2908	nuclear receptor subfamily 3 group C member 1	P04150
ANGPT2	285	angiopoietin 2	O15123
LGALS3	3958	galectin 3	P17931
LEP	3952	leptin	P41159
LCN2	3934	lipocalin 2	P80188
IL18	3606	interleukin 18	Q14116
IL10	3586	interleukin 10	P22301
IL6	3569	interleukin 6	P05231
IL1B	3553	interleukin 1 beta	P01584
IGF1	3479	insulin like growth factor 1	P05019
SIRT1	23411	sirtuin 1	Q96EB6
DLG2	1740	discs large MAGUK scaffold protein 2	Q15700
ALOX5	240	arachidonate 5-lipoxygenase	P09917
GABPA	2551	GA binding protein transcription factor subunit alpha	Q06546
GCG	2641	glucagon	P01275
GLP1R	2740	glucagon like peptide 1 receptor	P43220
IL1A	3552	interleukin 1 alpha	P01583
COX2	4513	cytochrome c oxidase subunit II	P00403
ACTB	60	actin beta	P60709
IL6R	3570	interleukin 6 receptor	P08887
MTCO2P12	107075310	MT-CO2 pseudogene 12	
CDKN2A	1029	cyclin dependent kinase inhibitor 2A	P42771
IL33	90865	interleukin 33	O95760
BGLAP	632	bone gamma-carboxyglutamate protein	P02818
PIK3CA	5290	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha	P42336
CXCL12	6387	C-X-C motif chemokine ligand 12	P48061
PIK3CB	5291	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta	P42338
PIK3CD	5293	phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta	O00329
SOST	50964	sclerostin	Q9BQB4
S100A9	6280	S100 calcium binding protein A9	P06702
CX3CR1	1524	C-X3-C motif chemokine receptor 1	P49238
MIR155	406947	microRNA 155	
HSD11B1	3290	hydroxysteroid 11-beta dehydrogenase 1	P28845
S100A12	6283	S100 calcium binding protein A12	P80511
MIR146A	406938	microRNA 146a	nan
CD40LG	959	CD40 ligand	P29965
HIF1A	3091	hypoxia inducible factor 1 subunit alpha	Q16665
CP	1356	ceruloplasmin	P00450
CXCL8	3576	C-X-C motif chemokine ligand 8	P10145
NAMPT	10135	nicotinamide phosphoribosyltransferase	P43490
MIR499A	574501	microRNA 499a	
NOS2	4843	nitric oxide synthase 2	P35228
SERPINA3	12	serpin family A member 3	P01011
CCR6	1235	C-C motif chemokine receptor 6	P51684

(*Continued*)

Table 1. Susceptibility Gene Shared by Cardiovascular Disease and Rheumatoid Arthritis (*Continued*)

Gene Symbol	Gene Identifier (ID)	Gene Full Name	Uniport
MIR223	407008	microRNA 223	
PTGS1	5742	prostaglandin-endoperoxide synthase 1	P23219
AKT1	207	AKT serine/threonine kinase 1	P31749
MIR150	406942	microRNA 150	
ICOSLG	23308	inducible T cell costimulator ligand	O75144
MIR132	406921	microRNA 132	
STAT3	6774	signal transducer and activator of transcription 3	P40763
IL17A	3605	interleukin 17A	Q16552
HSPD1	3329	heat shock protein family D (Hsp60) member 1	P10809
TLR2	7097	toll-like receptor 2	O60603

RESULTS

Identification and Selection of Shared Genes

Rheumatoid arthritis– and CVD-associated genes were retrieved from the DisGeNET and Malacards databases using defined thresholds. Specifically, 290 RA-related genes and 210 CVD-related genes were retrieved from the MalaCards database, and 787 RA-related genes and 433 CVD-related genes from the DisGeNET databases (Supplementary Table 1). Among these genes, 108 shared genes were identified between RA and CVD (Table 1). These shared genes comprise immune-related genes (e.g., *CDKN2A*, *ICAM1*, *IFNG*, *TNF*), oxidative stress-related genes (e.g., *LPA*, *HIF1A*, *NOS2*, *NOS3*), and interleukin-related genes (e.g., *IL6*, *IL10*, *IL1B*, *IL17A*, *IL18)*.

Functional Annotation of the Shared Genes

Gene ontology (GO) enrichment analysis was then performed on the 108 genes, which showed that 10 GO biological processes were significantly enriched (Supplementary Table 2). Among these processes, immune responses were the most significant, followed by secretion by cells, leukocyte activation, and immune effector process. Figure 1 showed the enrichment results for the biological process, cellular component (CC), and molecular function (MF) terms are shown. Notably, the significantly enriched categories included biological regulation, response to stimulus, and multicellular organismal processes. In the CC terms and MF terms, the enrichment items included extracellular space, membrane and nucleus, protein binding, ion binding, and nucleic acid binding.

Protein–Protein Interaction Network Construction for Shared Genes

A total of 6 gene modules (i.e., module 1-6) were generated after mapping all the shared genes onto the PPI network (Figure 2). These modules were mainly associated with key biological functions, including inflammatory response,

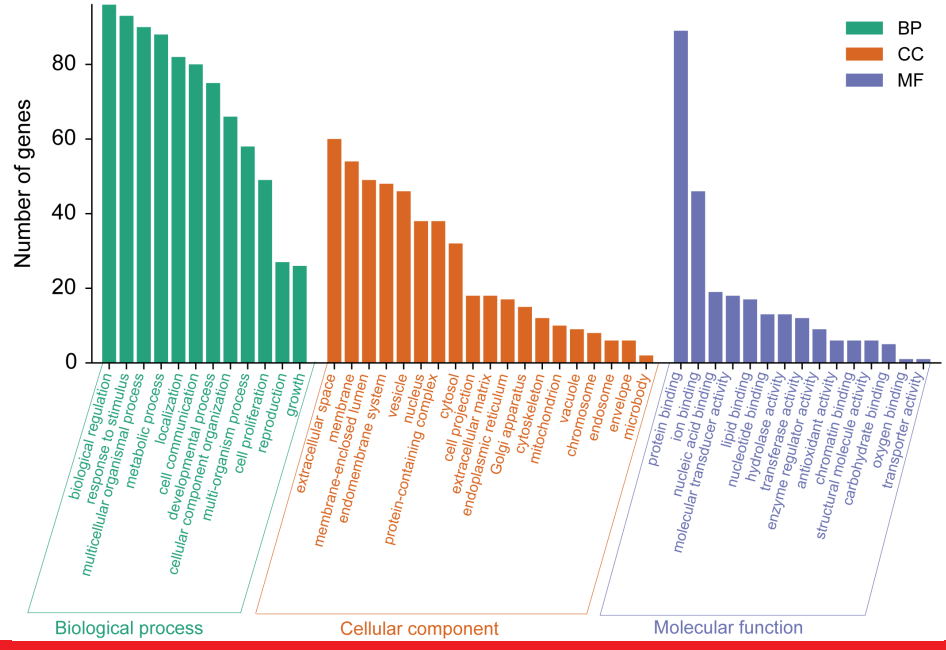


Figure 1. Functional enrichment analysis on the 108 shared genes between cardiovascular disease and rheumatoid arthritis. BP, biological process; CC, cellular component; MF, molecular function.

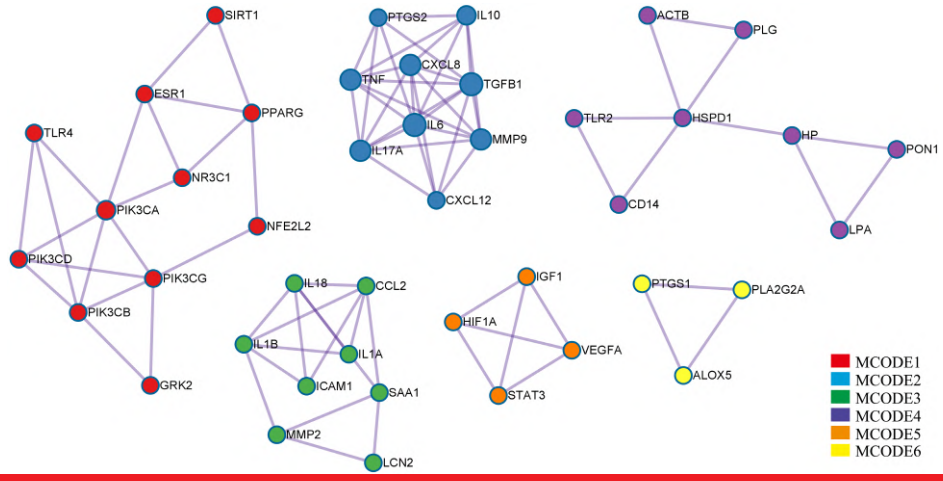


Figure 2. Six gene modules were generated after mapping all the shared genes onto the protein–protein interaction network.

interleukin signaling transmission, cytokine signaling transmission in the immune system, and lipid metabolism (Table 2).

Hub Genes Selection from the Interaction Network

As shown in Figure 3, 2554 pathway interactions involving 175 nodes were identified. Enriched pathways included lipids and atherosclerosis (AS) signaling, fluid shear stress and AS, as well as the RA and AS. Moreover, the results showed that the AGE-RAGE signaling pathway was enriched in diabetic complications, together with the HIF-1, TNF, and Toll-like receptor signaling pathways. Furthermore, 10 hub genes were identified from the network, including *IL-10*, *IL-1B*, *TNF*, *IL-6*, *AKT1*, *MMP9*, *CXCL8*, *ICAM1*, *VCAM1,* and *IL-1A*.

Pathway Enrichment of Rheumatoid Arthritis– and Cardiovascular Disease–Associated Genes

Pathway enrichment analysis revealed 69 significant pathways for RA and 48 for CVD (Supplementary Table 3). After overlapping these enriched pathways, 40 shared pathways were obtained (Supplementary Table 4). Some of the shared pathways were associated with the T cell receptor signaling pathway, B cell receptor signaling pathway, chemokine signaling pathway, and leukocyte trans-endothelial migration. In addition, others were associated with signaling transmission, such as the Janus kinase/signal transducer and activator of transcriptio (JAK-STAT) signaling pathway, mitogen-activated protein kinases (MAPK) signaling pathway, the cytokine-cytokine receptor interaction, as well as the endocrine system and cancer-related pathways.

Table 2. Gene Modules in the Protein–Protein Interaction Network of the Shared Genes

MCODE	GO Term or Pathway	Description	Log10(*P*)
MCODE_1	WP4483	Relationship between inflammation COX 2 and EGFR	−12.9
	WP5191	Resolvin E1 and resolvin D1 signaling pathways promoting inflammation resolution	−11.3
	R-HSA-9027276	Erythropoietin activates Phosphoinositide-3-kinase (PI3K)	−11.3
MCODE_2	WP5285	Immune infiltration in pancreatic cancer	−22.5
	R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	−18.7
	WP5095	Overview of pro-inflammatory and profibrotic mediators	−18.1
MCODE_3	R-HSA-6785807	Interleukin-4 and Interleukin-13 signaling	−19.7
	R-HSA-449147	Signaling by Interleukins	−14.5
	R-HSA-1280215	Cytokine Signaling in Immune system	−12.7
MCODE_4	M264	PID TOLL ENDOGENOUS PATHWAY	−7.6
	hsa05134	Legionellosis	−6.5
	GO:0032481	positive regulation of type 1 interferon production	−6.1
MCODE_5	hsa04066	HIF-1 signaling pathway	−9.8
	hsa05205	Proteoglycans in cancer	−8.7
	GO:0050679	positive regulation of epithelial cell proliferation	−8.6
MCODE_6	hsa00590	Arachidonic acid metabolism	−8.1
	R-HSA-556833	Metabolism of lipids	−4.8

GO, gene ontology.

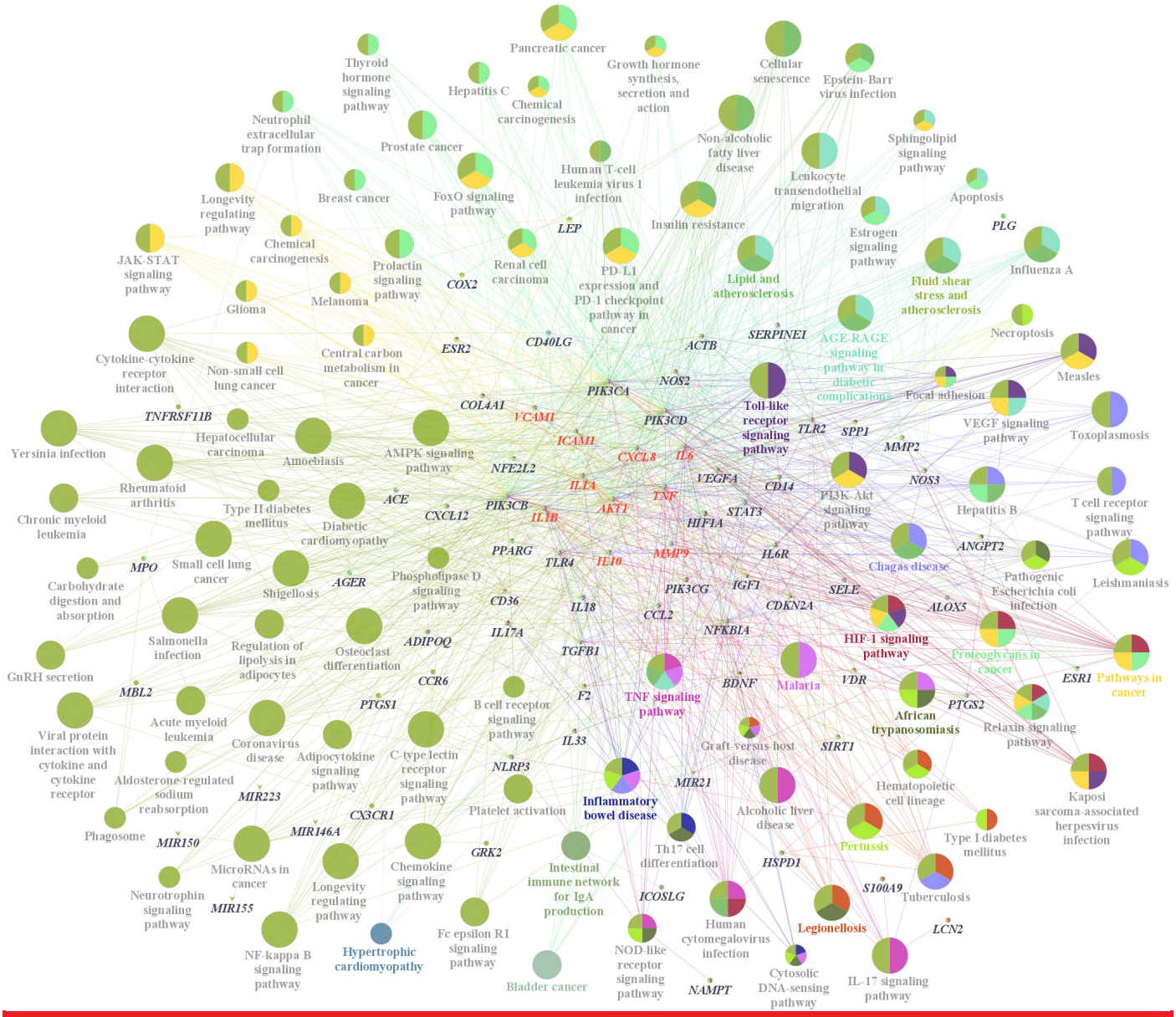


Figure 3. Pathway enrichment analysis and visualization of the hub genes between cardiovascular disease and rheumatoid arthritis. The network of interactions was generated with ClueGo and CluePedia. CytoHubba was utilized to predict the hub genes. Red genes represented the hub genes.

Pathway Cross-Talk Between Rheumatoid Arthritis and Cardiovascular Disease

Among the 40 shared pathways, 38 shared at least 3 genes with at least 1 other pathway and were included in the cross-talk analysis. Subsequently, a pathway interaction network was constructed based on shared genes to explore the underlying biological processes. In total, 52 out of the 108 shared genes were mapped to this network, resulting in 90 nodes and 734 edges (Figure 4). The network was classified into 4 functional modules, including the immune system, endocrine or metabolic system, cancer-related, and signaling transmission. Interestingly, these modules were interconnected through 1 or more key signaling pathways, suggesting coordinated biological relevance across disease mechanisms.

Selection of Candidate Genes Associated with Rheumatoid Arthritis and Cardiovascular Disease

All RA- and CVD-associated genes were mapped onto a PPI network, generating 957 nodes (540 RA-associated and 417 CVD-associated) and 9272 edges (2425 RA-associated and 6747 CVD-associated). Subsequently, a combined network including 867 nodes and 8973 edges was established to identify genes potentially linked to both diseases. According to the node degree, 42 candidate genes that were directly linked to the shared genes were selected with a score of 20 or more (Table 3). Among these genes, 21 genes showed direct association with 5 or more shared genes. In addition, 7 genes (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44)* showed direct association with 9 or more shared genes. The

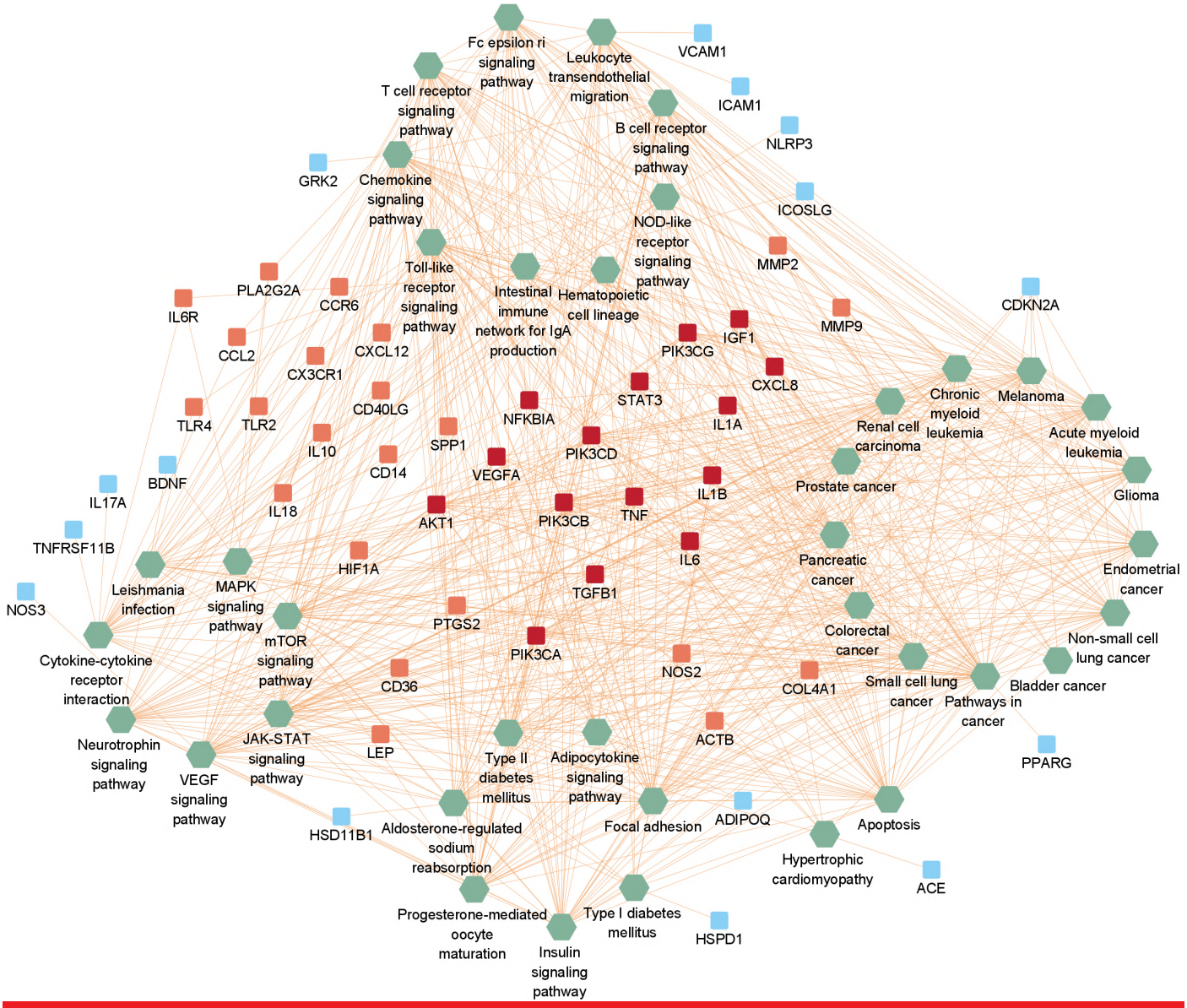


Figure 4. Pathway-pathway network of 108 shared genes between cardiovascular disease and rheumatoid arthritis. Green nodes represented pathways. Red nodes, pink nodes, and blue nodes represented genes linked to at least 3 modules, at least 2 modules, and 1 modules, respectively.

PPI network of the 7 selected candidate genes (Figure 5), which led to the generation of 102 nodes and 673 edges.

Expression Analysis of Candidate Genes from Databases

In this section, tissue- and cell-specific expression analyses of the 21 novel candidate genes were performed. All 21 novel candidate genes were RA-associated, suggesting that these genes may be involved in the molecular mechanisms of CVD. As shown in Figures 6 and 7, the *FN1*, *EGFR*, *JUN*, *CXCL1*, and *RELA* were extensively expressed in cardiac tissue. At the same time, *FN1*, *EGFR*, *JUN*, *CXCL1*, and *RELA* were extensively expressed in fibroblasts of cardiac tissue. Moreover, *CD44*, *ITGAM*, *CCL2*, *CCL4,* and *CCL3* were specifically expressed in leukocytes in cardiac tissue.

DISCUSSION

In this study, the 108 shared genes between CVD and RA were systematically analyzed. Functional enrichment analyses revealed that these shared genes are involved in immune responses, inflammatory signaling, cytokine activity, and lipid metabolism. Among them, inflammation-related and immune signaling pathways were particularly prominent. Based on degree centrality in the PPI network, 42 candidate genes were identified, of which 7 (i.e., *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44*) showed direct connections to 9 or more shared genes and were highlighted for further analysis.

Rheumatoid arthritis has been consistently associated with an elevated risk of CVD, which is a leading cause of mortality

Table 3. Forty-Two New Candidate Genes Related to Cardiovascular Disease and Rheumatoid Arthritis

Gene Symbol	Node Degree	Interact with Shared Genes
CD4	61	*CD40LG, IL10, IL17A, ICAM1, TNF, IL6, IL1B, TLR4*
IFNG	61	*IL1B, IL10, TNF, IL6, IL17A, IL1A, IL18, TLR4, TLR2, STAT3*
NFKB1	42	*TNF, TLR4, TLR2, NLRP3, PPARG, STAT3, NFKBIA, SIRT1*
CCL5	39	*IL10, TNF, IL6, CXCL12, CX3CR1, CCR6, CXCL8, IL1B, IL1A*
JAK1	38	*PIK3CB, PIK3CD, STAT3, PIK3CA*
CXCL10	37	*CXCL12, CXCL8, TLR4, TNF, IL10, IL6, IL1B, IL1A, TLR2*
CXCR4	36	*HIF1A, IL6, DPP4, F2, VCAM1*
FN1	36	*SPP1, TLR4, TNF, LCN2, IGF1, IL6, PLG, VCAM1, ICAM1, STAT3, TLR2, LGALS3, TGFB1*
IL4	35	*IL6, TNF, STAT3, IL6R*
EGFR	33	*PIK3CB, IGF1, ESR1, IL6, PIK3CD, HIF1A, STAT3, PIK3CA, TLR2, LGALS3, TGFB1*
JAK2	33	*PIK3CB, PIK3CD, LEP, STAT3, PIK3CA*
IL2	32	*IL6, TNF, IL6R*
CXCL1	32	*IL6, TNF, CXCL12, IL10, IL17A, CXCL8, IL18, IL1B, IL1A*
PTPN11	32	*STAT3*
JUN	32	*TNF, NFE2L2, STAT3, NR3C1, NFKBIA, SIRT1*
RELA	31	*TNF, TLR4, STAT3, TLR2, SIRT1*
STAT1	31	*STAT3*
CD40	30	*TNF, TLR4, IL10, CD40LG, ICOSLG, ICAM1, IL1B, TLR2*
JAK3	28	*PIK3CB, PIK3CD, STAT3, PIK3CA*
CCL4	28	*IL10, TNF, IL6, CXCL12, CCR6, CXCL8, IL1B, IL1A*
CCR2	28	*CXCL8, CXCL12, CCR6*
MYD88	28	*TNF, TLR4, TLR2, NFKBIA*
LOC102723407	28	*PLG*
CCL20	26	*CXCL12, IL6, TNF, CX3CR1, CCR6, CXCL8, IL1B*
CD44	26	*CXCL12, SPP1, COL4A1, TLR4, MMP9, SELE, VCAM1, ICAM1, LGALS3, MMP2*
CD28	25	*CD40LG, ICOSLG, PIK3CD, IL10, PIK3CB, ICAM1, PIK3CA*
CCL3	25	*IL10, TNF, IL6, CX3CR1, CCR6, CXCL8, IL1B, IL1A*
CCR5	25	*CXCL12, CXCL8*
CXCL2	25	*TNF, IL6, CXCL8, IL1B, IL1A*
CCR1	24	*CXCL8, CXCL12, CCR6*
CCR7	24	*CXCL12, CXCL8*
CSF2	24	*IL6, CXCL8, TNF, IL10, IL1B, IL1A*
SYK	23	*TLR4*
CD80	23	*ICAM1, IL10, TNF*
MAPK3	23	*TNF*
MAPK1	23	*STAT3*
CCR3	21	*CXCL12, CCR6, CXCL8*
MAPK8	21	*STAT3*
CHUK	21	*TNF, NFKBIA*
CTLA4	20	*IL10, LCN2, ICOSLG*
CD86	20	*IL10, TNF, ICAM1*
ITGAM	20	*PIK3CB, TNF, PIK3CD, TLR4, VCAM1, PIK3CA*

in this population.[23] This may be attributed to the chronic inflammatory state characteristic of RA, which is marked by elevated levels of circulating inflammatory mediators and endothelial dysfunction.[24,25] This in turn, may promote the AS and cardiomyocyte dysfunction, thereby increasing the risk of CVD, MI, and congestive heart failure.[26] The understanding of how susceptibility genes contribute to the interplay between CVD and RA is still limited. To address this, a systematic analysis of the shared genes was conducted between CVD and RA. Enriched analysis identified key pathways, including lipids and AS signaling, fluid shear stress and AS, as well as the RA and AS. These findings highlight

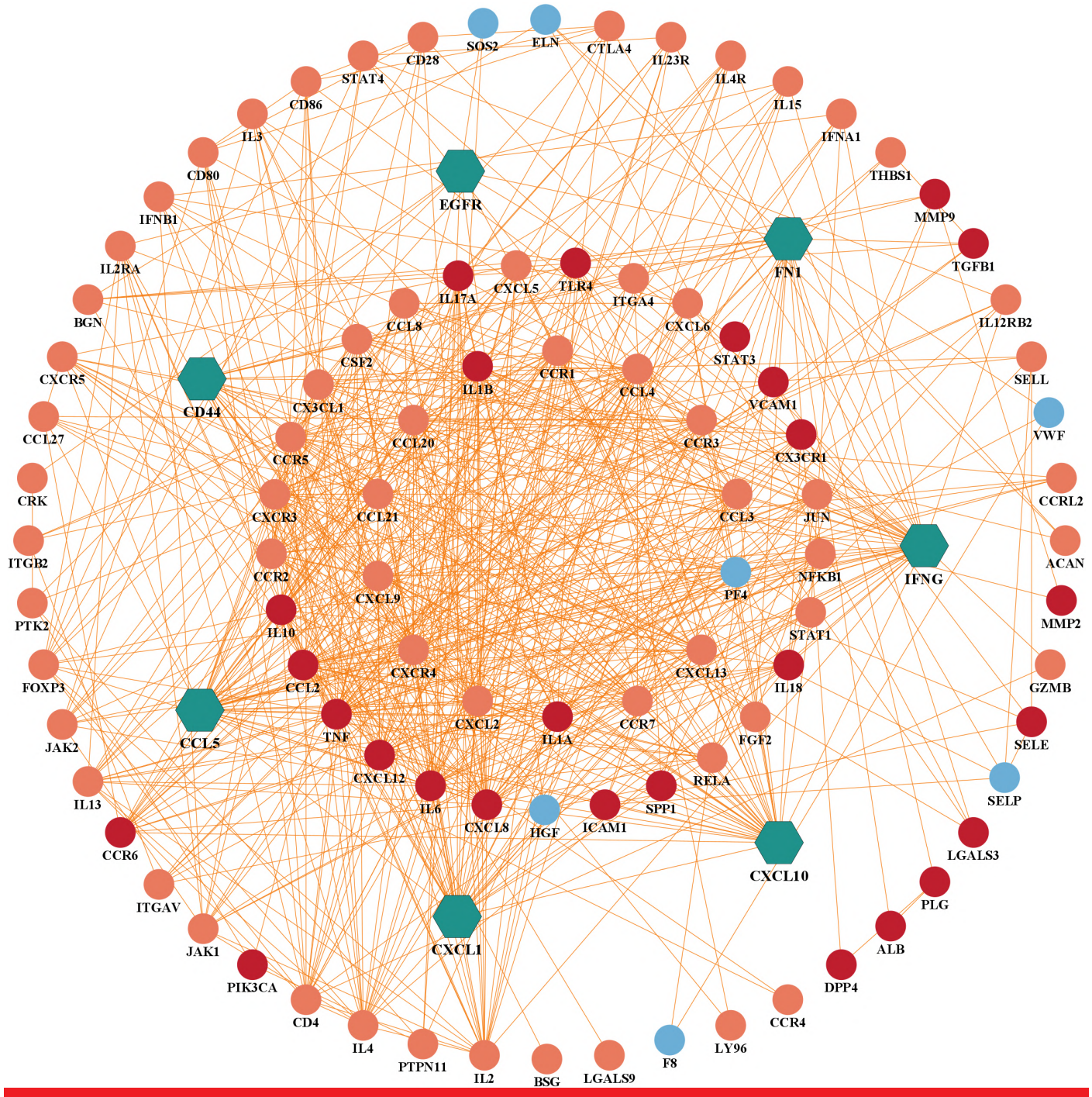


Figure 5. Protein–protein interaction network of the 7 candidate genes. Green nodes represented the candidate genes. Red nodes represented the shared genes. The blue and pink nodes represented the cardiovascular disease–associated and rheumatoid arthritis–associated genes.

potential molecular mechanisms underlying the increased CVD risk in RA patients and may guide future therapeutic strategies targeting shared pathogenic pathways.

Chronic inflammation is a central feature in the pathogenesis of both RA and CVD.[27] Lipid abnormalities, particularly the impaired atheroprotective function of high-density lipoprotein, are recognized as key contributors to the increased risk of atherosclerotic cardiovascular disease in RA patients.[28] Consistently, the shared gene modules in the PPI network encompassed interleukin signaling, cytokine-cytokine receptor interaction, and pathways regulating inflammation resolution. Additionally, pathways related to lipid metabolism and arachidonic acid were significantly enriched, supporting evidence that altered lipid profiles and inflammatory lipoproteins contribute to the pathogenesis of CVD in RA

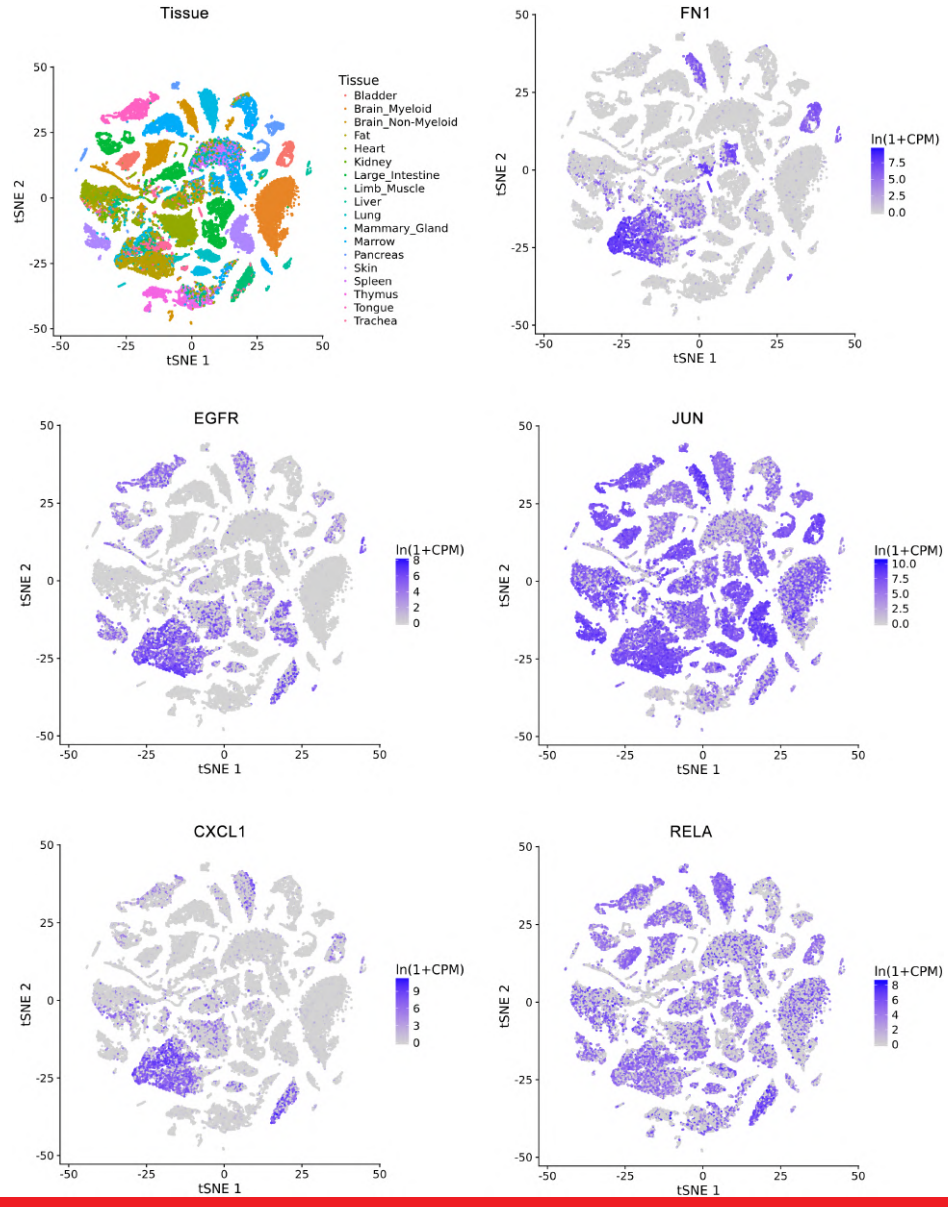


Figure 6. Expression analysis of candidate genes in different tissues.

patients.[29,30] These findings reinforce that inflammation and lipid dysregulation may constitute shared pathological mechanisms driving CVD in the context of RA.

To elucidate key molecular players bridging RA and CVD, we constructed a combined PPI network was constructed and candidate genes were identified based on their connectivity to shared disease-associated genes. Notably, 7 candidate genes that were found showed a direct link to at least 9 genes, including *IFNG*, *CCL5*, *CXCL10*, *FN1*, *EGFR*, *CXCL1*, and *CD44*. These genes have well-established roles in immune regulation and inflammation. *IFNG* encodes interferon-gamma (IFN-γ), a key cytokine secreted by both innate and adaptive immune systems. Variants in *IFNG* have been associated with increased susceptibility to infections and autoimmune diseases,[31] both of which are implicated in the pathogenesis of RA and CVD.[32,33] These findings suggest that *IFNG* may be involved in CVD and RA by regulating immune responses and inflammatory pathways. *CCL5* encodes a member of the chemokine superfamily involved in immunoregulatory and inflammatory processes.[31] *CCL5*-related ankylosing spondylitis was associated with hypertension and the development of obesity, both of which were common risk factors for CVD.[34] *CXCL1* is also associated with inflammation and the accumulation of neutrophils. In CVD, *CXCL1* was crucial in cardiac fibrosis, especially induced by atrial fibrillation, post-irradiation, as well as hypertension.[35] Likewise, the role of *CXCL10* in CVD has been extensively described,[36] particularly in promoting immune cell infiltration via CXCR3. Additionally, Lee et al[37] demonstrated that *CXCL10* signaling through CXCR3 and TLR4 enhances inflammatory cell migration, potentially contributing to the progression of RA.

Notably, *FN-1* has been identified as a key gene associated with RA onset.[38] Using bioinformatics methods, Xiong et al[39] identified *FN-1* as a novel biomarker for aortic valve

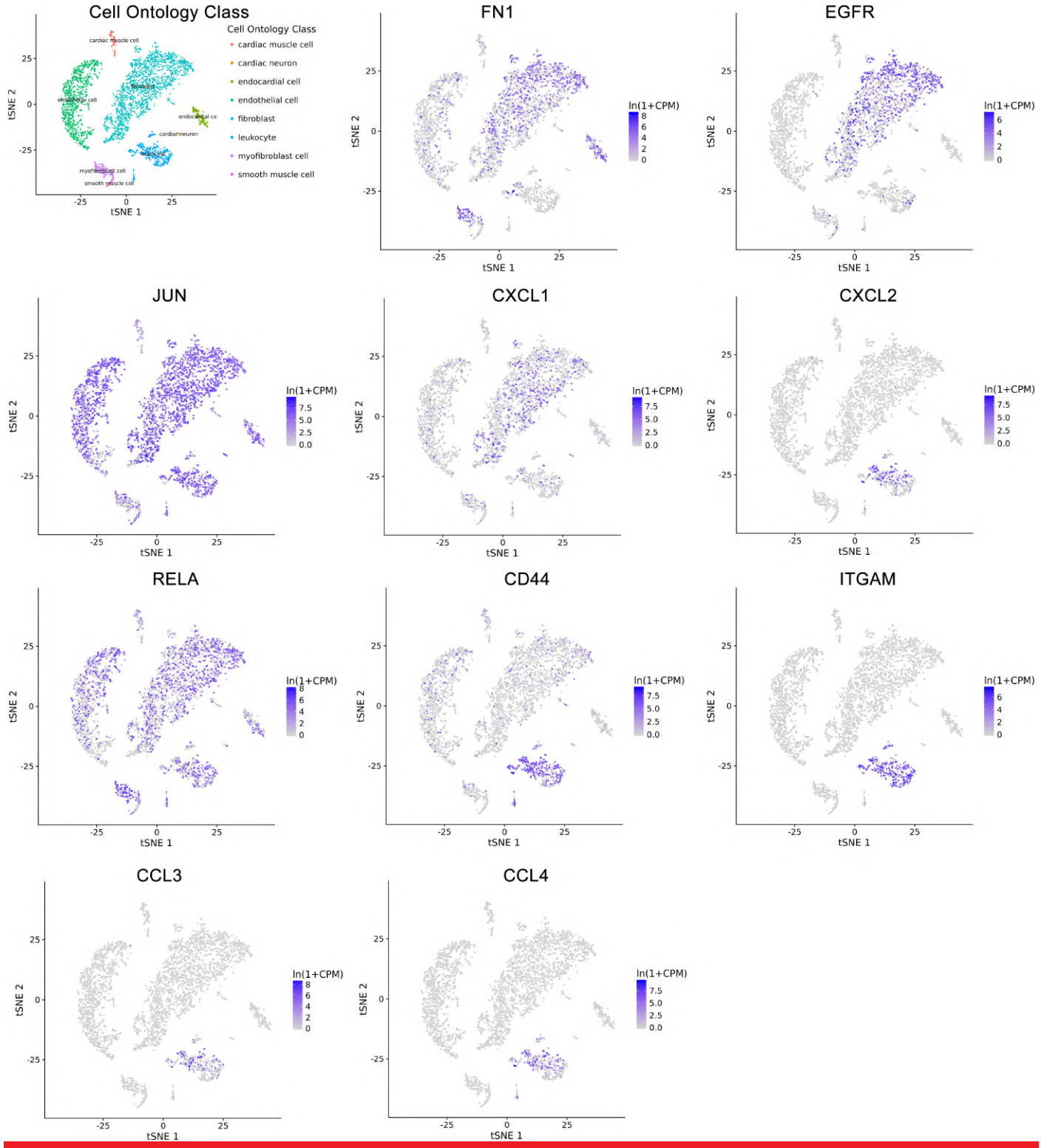


Figure 7. Expression analysis of candidate genes in different cell types.

calcification, an important event in the development of CVD. In a mouse model of collagen-induced arthritis, *FN-1* expression was linked to over a 3-fold increased risk of RA, further supporting its role in disease pathogenesis.[40] The EGFR family and its ligands function as central regulators of multiple cellular processes. Epidermal growth factor receptor (EGFR) signaling is essential for cardiac development and remodeling and has been proposed as a therapeutic target in CVD.[41] Additionally, *EGFR* contributes to synovial hyperplasia in RA through its roles in angiogenesis and tissue regulation.[42,43] *CD44* expression is significantly elevated in diseased arterial tissues and inflammatory cytokine-stimulated endothelial

cells.[44] The CD44-hyaluronic acid axis plays a critical role in inflammatory responses and AS pathogenesis, suggesting its potential as a therapeutic target for CVD.[45] In RA, *CD44* is highly expressed in inflamed synovial tissues compared to normal synovium, indicating its relevance in disease progression and its potential for targeted drug delivery.[46]

These 7 candidate genes represent potential molecular links between CVD and RA and may serve as future therapeutic targets. However, it is important to note that these findings are based on bioinformatics and in silico predictions. Functional validation is needed through experimental models and clinical cohorts to confirm causality and therapeutic relevance. In particular, interventions targeting *IFNG* or *EGFR* signaling could be explored for dual impact on inflammation and cardiovascular outcomes in RA patients. Similarly, modulation of chemokines such as CCL5 and CXCL10 may help reduce both synovial and vascular inflammation.

There are some limitations in this study. First, the analysis relied on publicly available databases, which may introduce biases or incomplete gene annotations. Second, the current human interactome is still not complete, and there might be some errors despite significant improvement in the quality of PPI databases. Third, the functional roles of candidate genes require further experimental validation, such as gene knockout or overexpression studies.

CONCLUSION

This study identified 108 shared genes between CVD and RA, with enrichment analyses highlighting their roles in immune and inflammatory processes. Among these, 7 candidate genes were considered as potential key mediators in the shared pathogenic mechanisms. These findings provide new insights into common molecular mechanisms and may offer promising targets for future diagnostic or therapeutic strategies.

Data availability statement: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Committee Approval: All data used in this study are publicly available, and studies are approved by relevant review boards and conducted according to the Declaration of Helsinki, with written informed consent from all participants. No additional ethical approval was required.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception and design: Yaobang Bai, Yunpeng Bai, Nan Jiang; database search and data extraction: Yaobang Bai, Yunpeng Bai; study evaluation: Zhenhua Wu, Qingliang Chen; planned and conducted the statistical analysis: Yaobang Bai, Zhenhua Wu; drew all the figures and tables: Yunpeng Bai, Qingliang Chen; drafted the manuscript: Yaobang Bai, Yunpeng Bai; corrected and validated the manuscript: Nan Jiang. All authors read and approved the final manuscript.

Declaration of Interests: The authors have no conflicts of interest to declare.

Funding: This work was supported by the Tianjin Key Medical Discipline (Specialty) Construction Project (grant no. TJYXZDXK-042A).

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Supplementary Table 1. Rheumatoid arthritis related genes from DisGeNET

Supplementary table can be accessed by clicking **here.**

Supplementary Table 2. The GO biological processes significantly enriched in the 108 shared genes between RA and CVD

Gene Set	Description	Size	Expect	Ratio	P Value	FDR
GO:0006955	immune response	1919	10.202	5.2932	<2.2e-16	<2.2e-16
GO:0046903	secretion	1605	8.5326	5.9771	<2.2e-16	<2.2e-16
GO:0032940	secretion by cell	1472	7.8255	6.006	<2.2e-16	<2.2e-16
GO:0001775	cell activation	1335	7.0972	6.9042	<2.2e-16	<2.2e-16
GO:0045321	leukocyte activation	1184	6.2944	6.8314	<2.2e-16	<2.2e-16
GO:0002252	immune effector process	1141	6.0658	6.5943	<2.2e-16	<2.2e-16
GO:0002443	leukocyte mediated immunity	760	4.0403	8.6626	<2.2e-16	<2.2e-16
GO:0002263	cell activation involved in immune response	697	3.7054	7.8264	<2.2e-16	<2.2e-16
GO:0002366	leukocyte activation involved in immune response	693	3.6841	7.8716	<2.2e-16	<2.2e-16
GO:0002274	myeloid leukocyte activation	634	3.3705	8.3074	<2.2e-16	<2.2e-16

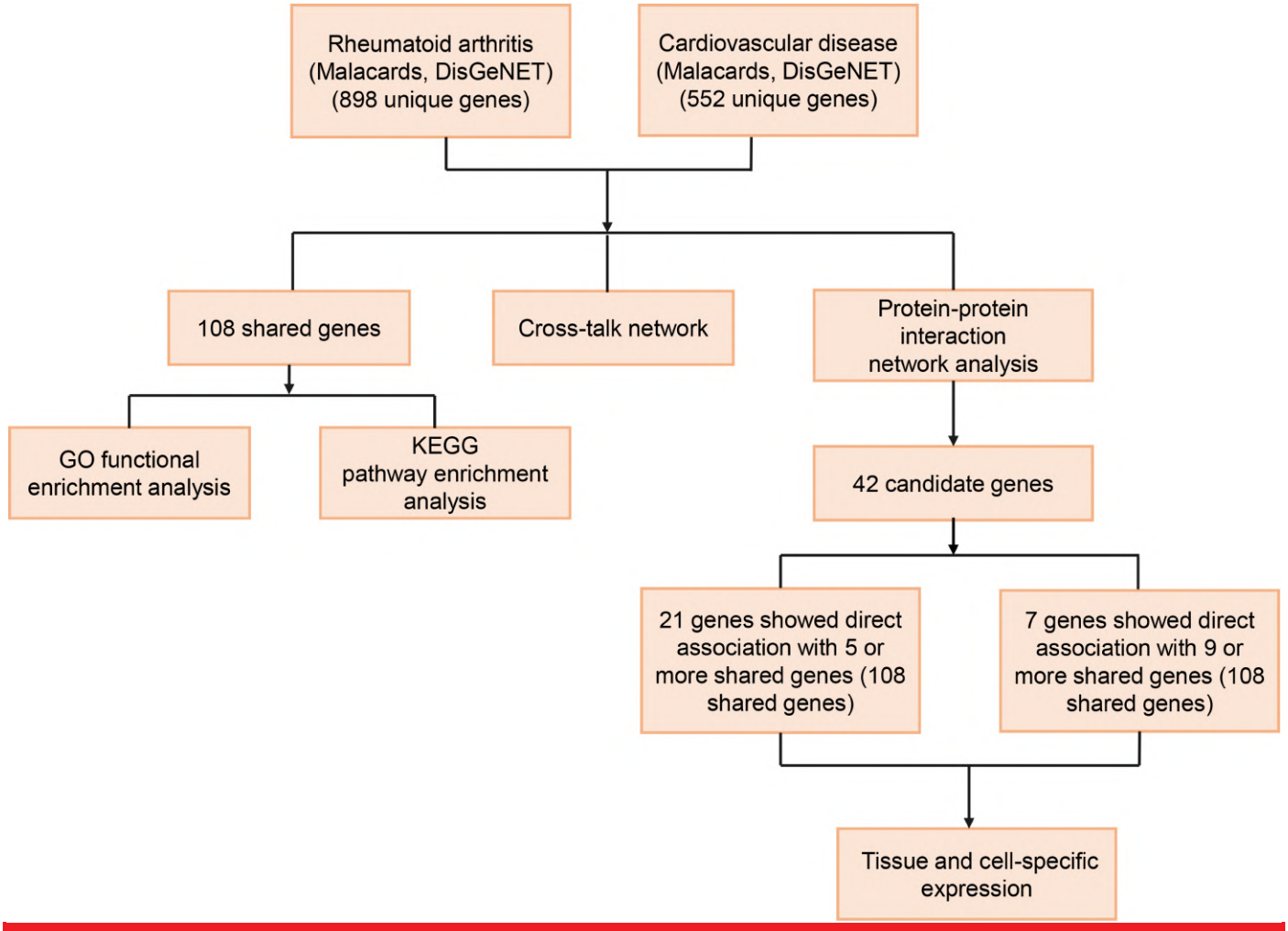
Supplementary Table 3. 69 significantly enriched pathways of RA.

XXX

Supplementary Table 4. 40 shared pathways related to RA and CVD

Category	Name	ID
Pathway	KEGG_COMPLEMENT_AND_COAGULATION_CASCADES	M16894
Pathway	KEGG_ADIPOCYTOKINE_SIGNALING_PATHWAY	M10462
Pathway	KEGG_ALDOSTERONE_REGULATED_SODIUM_REABSORPTION	M16473
Pathway	KEGG_PATHWAYS_IN_CANCER	M12868
Pathway	KEGG_TYPE_II_DIABETES_MELLITUS	M19708
Pathway	KEGG_CHEMOKINE_SIGNALING_PATHWAY	M4844
Pathway	KEGG_TOLL_LIKE_RECEPTOR_SIGNALING_PATHWAY	M3261
Pathway	KEGG_MTOR_SIGNALING_PATHWAY	M7561
Pathway	KEGG_HYPERTROPHIC_CARDIOMYOPATHY_HCM	M8728
Pathway	KEGG_LEISHMANIA_INFECTION	M3126
Pathway	KEGG_VEGF_SIGNALING_PATHWAY	M1749
Pathway	KEGG_CYTOKINE_CYTOKINE_RECEPTOR_INTERACTION	M9809
Pathway	KEGG_RENAL_CELL_CARCINOMA	M13266
Pathway	KEGG_ACUTE_MYELOID_LEUKEMIA	M19888
Pathway	KEGG_MELANOMA	M15798
Pathway	KEGG_CHRONIC_MYELOID_LEUKEMIA	M321
Pathway	KEGG_FC_EPSILON_RI_SIGNALING_PATHWAY	M11816
Pathway	KEGG_ENDOMETRIAL_CANCER	M19877
Pathway	KEGG_LEUKOCYTE_TRANSENDOTHELIAL_MIGRATION	M2164
Pathway	KEGG_PANCREATIC_CANCER	M9726
Pathway	KEGG_APOPTOSIS	M8492
Pathway	KEGG_JAK_STAT_SIGNALING_PATHWAY	M17411
Pathway	KEGG_PROSTATE_CANCER	M13191

Category	Name	ID
Pathway	KEGG_T_CELL_RECEPTOR_SIGNALING_PATHWAY	M9904
Pathway	KEGG_FOCAL_ADHESION	M7253
Pathway	KEGG_NOD_LIKE_RECEPTOR_SIGNALING_PATHWAY	M15569
Pathway	KEGG_COLORECTAL_CANCER	M14631
Pathway	KEGG_GLIOMA	M1835
Pathway	KEGG_SMALL_CELL_LUNG_CANCER	M3228
Pathway	KEGG_NON_SMALL_CELL_LUNG_CANCER	M19818
Pathway	KEGG_INSULIN_SIGNALING_PATHWAY	M18155
Pathway	KEGG_HEMATOPOIETIC_CELL_LINEAGE	M6856
Pathway	KEGG_B_CELL_RECEPTOR_SIGNALING_PATHWAY	M5436
Pathway	KEGG_MAPK_SIGNALING_PATHWAY	M10792
Pathway	KEGG_VASCULAR_SMOOTH_MUSCLE_CONTRACTION	M9387
Pathway	KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	M615
Pathway	KEGG_PROGESTERONE_MEDIATED_OOCYTE_MATURATION	M3578
Pathway	KEGG_NEUROTROPHIN_SIGNALING_PATHWAY	M16763
Pathway	KEGG_BLADDER_CANCER	M19096
Pathway	KEGG_TYPE_I_DIABETES_MELLITUS	M12617



Supplementary Figure 1. The flow diagram of study design.