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In Silico Identification of Interaction between Ageing and Cardiovascular Disease Genes

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Abstract

Heart is the central organ that pumps pure blood to whole body through blood vessels. This circulation system involves functioning of large number of genes that interacts for proper functioning. Any malfunctioning of single gene leads to the cardiovascular diseases (CVDs) Aging is an inevitable part of life and unfortunately the risk of CVDs increases with ageing. Although numerous studies were carried on cardiovascular diseases that considered both young and aged humans, but still there are many unanswered questions as to how the genetic pathways that regulate aging influence cardiovascular disease and vice versa. Therefore, this is of great interest to identify the interaction between cardiovascular diseases and ageing genes. Genes for CVDs and ageing were collected from various databases and a network was created for their common genes. Network in analyzed to find the interaction between ageing and cardiovascular disease genes.

Keywords: Cardiovascular disease; Ageing; Interaction; Genes; Network; Databases; Nodes; Health

Introduction

The most important factor of cardiovascular disease is a person's age. It is estimated that by 2030, approximately 20% of the population will be aged 65 or older. In this age group, CVD will result in 40% of all deaths and rank as the leading cause [1]. The fields of cardiovascular disease and aging have remained largely separate. However, now this gap is beginning to close and these two fields are merging together. But still there are many unanswered questions as to how the aging genes are accessible to CVDs and are interacting with each other [2].

CVDs risk increases with age but now many factors like nutrition, role of social status and psychological stress is much modulating CVD risk [3]. Costantino et al. reported that in the near future there will be more exponential increase in the prevalence of CVD due to due to daily living activities. It is a fact that additional 27 million people will have hypertension, 8 million coronary heart diseases, 4 million strokes and 3 million heart failures [4]. So, there is an urgent need complete understanding of the mechanisms of ageing the affects the CVD risk. In present study, we tried to identify the gene interaction of ageing and CVDs.

CVDs are diseased heart conditions that include variety of diseases associated with diseased vessels, structural problems in heart and blood vessels and blood clots. Some of the common cardiovascular diseases are that we have included in our study are coronary heart disease, cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, pulmonary embolism, cardiomyopathy, cardiac arrhythmia, hypertension, cardiac arrest, congestive heart disease, cardiac conduction disease, valvular heart diseases, aortic aneurysm, myocardial infarction, atherosclerosis and acute coronary syndrome.

In this study, we create a network of above mentioned CVDs and ageing genes to find the common interaction of both. This finding will help in further understanding of this disease interaction at molecular level. For this purpose we created two *in silico* networks, one for cardiovascular diseases and another for ageing. Both networks are compared for their biological pathways involved. Identified genes from common pathways are further used to create a network of ageing and cardiovascular diseases. The resultant network is then analyzed for important nodes in terms of degree and betweenness.

Methodology

Collection of genes for CVDs and ageing

Genes for CVDs were collected from publicly available databases such as OMIM (https://www.omim.org/) [5], PubMed Central (PMC-https://www.ncbi.nlm.nih.gov/pmc/) and PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) [6]. This was done through text mining using diseases specific keywords and their relevant genes. Ageing genes were retrieved from GenAge database (http://genomics.senescence.info/genes/) maintained at Human Ageing Genomic Resources (HAGR) http://genomics.senescence.info/) [7].

Network creation for CVDs and ageing genes

The network for genes of CVDs and ageing was created using Pathway Commons Network Visualizer (PCViz) available online at http://www.pathwaycommons.org/pcviz/ [8]. We opted to choose only "paths-between" interactions as it consider interactions of direct paths/edges to the queried node.

Pathway analysis

The Reactome pathway database available at http://www.reactome.org was used to explore the pathways of CVDs and ageing [9]. Common pathways were used to manually identify common genes of CVDs and ageing.

Common gene network analysis

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Common network of CVD and ageing was created using STRING available at https://string-db.org/ [10]. It includes both physical (direct) and functional (indirect) associations. For each node of the network betweenness centrality is calculated using cytoscape [11]. It is the measure of centrality of a node in the network to find the important nodes of the network. Betweenness centrality for node *x*, is calculated by summing the number of shortest paths between pairs of nodes that pass through node *x* divided by the total number of shortest paths between pairs of nodes. It characterizes the control of a node over the information flow of the network. A node is considered important for a network if it appears on many paths that connect pairs of nodes. The node with higher value acts as a bridge between pairs of nodes in the network [12].

Results and Discussion

A total of 410 genes of CVDs were collected from OMIM, PubMed and PMC. Similarly, total 305 genes of ageing and were collected from GenAge database. Table 1 shows the list of genes used for the analysis.

From 410 genes of CVDs, related genes were eliminated as they are showing common interactions. For the leftover 339 genes of CVDs and 305 genes of ageing, network is created using PCViz and is analyzed. Figure 1 shows the network of CVDs. A total of 339 genes were input and network was created for 1171 genes which were neighbourhood genes with 5538 interactions. Similarly, for ageing a total of 305 genes were input and network was created for 1194 genes which were neighbourhood genes with 22795 interactions.

The above network is analysed by Reactome. The result shows

CVD Genes						
MEF2A	ARH	PPARG2	MRPS6	ANKS1A	IFNW1	COL4A1
CYP27A1	ABCA1	ADIPOQ	PON2	T CF21	IFNA21	COL4A2
ST6GALNAC5	LCAT	FABP4	HNF1A	ADT RP	ABO	HHIPL1
LRP6	APOC2	PLA2G7	MRAS	KCNK5	LIPA	ADAMT S7
LDLR	SELE	KLF14	LPA	PLG	KIAA1462	FURIN
PCSK9	GLUL	INSIG1	KDR	ZC3HC1	CYP17A1	FES
APOB	IL10	ABCG1	IL6R	HDAC9	CNNM2	SMG6
GIP	ABCG5	APOC3	ZEB2	LPL	NT 5C2	SRR
VAMP5	EDNRA	CX3CL1	IL18	T RIB1	PDGFD	RASD1
VAMP8	SLC22A4	GP1BA	ACT A2	GAT A2	ZPR1	PEMT
GGCX	CET P	ATP5G1	HMOX1	CX3CR1	APOA5	UBE2Z
ABCG8	MT HFR	SNF8	SCARB1	IT PKC	APOA4	AGT
F7	CCL2	SF3A2	CD36	UGT 1A1	APOA1	SELP
OLR1	CCR2	AP3D1	CRP	SERPINE1	BRAP	LRP8
T HBD	NOS3	DOT 1L	KALRN	KL	BCAP29	APOA2
IT GB3	FABP2	APOE	PAPPA	ANGPT L4	BT N2A1	F13B
IT GA2	ACE1	APOC1	PLCL2	MMP3	IRX1	T HBS4
CD40LG	EDN1	IRS1	GCLC	GSBS	LIPI	CDKN2A
KCNQ1	T NF	CX37	CACNB2	ABCC9	IT IH4	CDKN2B
CALM2	T GFB1	MIAT	SCN1B	SCN2B	LT A	SLC5A3
KCNH2	PSMA6	GCLM	SCN3B	NUP155	GHR	SH2B3
KCNE1	SNT A1	T NFSF4	HCN4	RYR2	EPHX2	LT A4H
KCNE2	KCNE3	F13A1	KCND3	CASQ2	T NNC1	ALOX5AP
SCN5A	KCNJ2	MYLK2	GJA5	T ECRL	T CAP	T MPO
ANK2	CAV3	T NNT 2	NPPA	T RDN	VCL	SLC22A5
KCNJ5	SCN4B	T PM1	RBM20	DPP6	FLNC	CRYAB
ALG10	AKAP9	MYBPC3	FKT N	KCNJ8	MYOZ2	PIGT
CALM1	CNBP	PRKAG2	EYA4	GPD1L	LDB3	LAMA4
CACNA1C	FLT 1	MYL3	PSEN1	T AB2	JPH2	RPS6KA3
LMNA	CT NNA3	T T N	DNAJC19	GAT A6	T LL1	PRDM16
PKP2	DES	MYL2	GAT AD1	ZIC3	PLN	T MEM87B
DSP	T AZ	ACT C1	PSEN2	CIT ED2	MYH7	SLC8A1
JUP	DMD	CSRP3	RAF1	GJA1	NEXN	LAMP2
DSG2	SGCD	NR2F2	SDHA	NKX2-5	MYPN	NFKB1
T GFB3	T MEM43	CHD7	SALL4	T BX20	WDPCP	T T R
DSC2	GNB3	JAG1	T BX1	BMPR2	CBL	GDF1
RIT 1	SCNN1A	B3GAT 3	KMT 2D	ECE1	DT NA	LZT R1
BRAF	AGT R1	T KT	KDM6A	ADD1	ZFPM2	SHOC2
SOS2	CYP11B2	T BX5	EVC2	CYP3A5	PIGL	NRAS
WNK1	NR3C2	HRAS	EVC	NOS2	MKKS	T FAP2B
WNK4	CYP11B1	MAP2K1	F2	PT GIS	ARHGAP31	PRDM6

HSD11B1	SCNN1B	MAP2K2	F5	AT P1B1	CRELD1	NKX2-6
SLC9B1	RGS5	SEMA3E	HABP2	KNG1	WRB	PT PN11
KCNMB1	ACVRL1	ESR1	F9	FGG	ADAMTS1	KRAS
MEX3C	KCNK3	ATHS	PROS1	HIVEP1	CYBA	SOS1
G6PC3	DGUOK	SOAT1	PROC	STXBP5	VEGFA	TNNI3K
SARS2	DYRK1B	LIPG	SERPINC1	VWF	FOXO1	PTRF
CPS1	SORT1	CD5L	PROZ	F11	FGB	DMPK
SMAD9	CACNA1H	ADAMTS4	SERPINA10	CYP4V2	SIRT1	GATA5
PDE3A	PEE1	IL6	IL1B	TFPI	FLNA	ALK2
AKAP10	CAV1	P2RY12	ALDH2	MIF	NOTCH1	RUNX2
EMD	LIPC	ICAM1	EGFR	MMP1	SMAD6	LRP1
TRPM4	HP	MBL2	IL1R1	SLC39A2	DCHS1	ADRB1
CLCNKA	FBN1	FCN2	CTLA4	MAGP2	KLK1	ADRA2C
ADA	LOX	TLR2	MASP2	BGN	TIMP2	GRK5
ADRB2	TGFBR1	TGFB2	MYH11	MLCK	MMP9	IL17RA
HSPB27	TGFBR2	COL3A1	PRKG1	MMP2	EFEMP2	IL17A
FRMD4B	SMAD3	FOXE3	MFAP5	MAT2A	TIMP3	
Ageing Genes						
A2M	BDNF	LEP	MYC	CREB1	EFEMP1	ESR1
ABL1	BLM	LEPR	NBN	CREBBP	EGF	FEN1
ADCY5	BMI1	LMNA	NCOR1	CSNK1E	EGFR	FGF21
AGPAT 2	BRCA1	LMNB1	NCOR2	CT F1	EGR1	FAS
AGT R1	BRCA2	LRP2	NFE2L1	CT GF	EIF5A2	FGF23
AIFM1	BUB1B	MAP3K5	NFE2L2	CT NNB1	ELN	FGFR1
AKT 1	BUB3	MAPK14	NFKB1	DBN1	EMD	FLT 1
APEX1	C1QA	MAPK3	NFKB2	DDIT 3	EP300	FOS
APOC3	CACNA1A	MAPK8	NFKBIA	DGAT 1	EPOR	FOXM1
APOE	CAT	MAPK9	NGF	DLL3	EPS8	FOXO1
APP	CCNA2	MAPT	NGFR	E2F1	ERBB2	FOXO3
APT X	CDC42	MAX	NOG	EEF1A1	ERCC1	FOXO4
AR	CDK1	MDM2	NR3C1	EEF1E1	ERCC2	GCLC
ARHGAP1	CDK7	MED1	NRG1	EEF2	ERCC3	GCLM
ARNT L	CDKN1A	MIF	NUDT 1	PIK3R1	ERCC4	GH1
AT F2	CDKN2A	MLH1	PAPPA	PIN1	ERCC5	GHR
AT M	CDKN2B	MSRA	PARP1	PLAU	ERCC6	GHRH
AT P5O	CEBPA	MT -CO1	PCK1	PLC2	ERCC8	GHRHR
AT R	CEBPB	MT 1E	PCMT 1	PMCH	PRDX1	GPX1
BAK1	GRN	MT OR	PCNA	PML	PRKCA	GPX4
BAX	GSK3A	MXD1	SIRT 1	POLB	PRKCD	
BCL2	GSK3B	MXI1	SIRT 3	POLD1	PRKDC	GRB2
BSCL2	GSR	HESX1	SIRT 6	POLG	PROP1	HT T
RB1	GSS	HIC1	SIRT 7	POLA1	PSEN1	IGF1
RECQL4	GST A4	HIF1A	SLC13A1	PON1	PT EN	IGF1R
RELA	GST P1	HMGB1	SNCG	PPARA	PT GS2	IGF2
RET	GT F2H2	HMGB2	SOCS2	POU1F1	PT K2	IGFBP2
RGN	H2AFX	HOXB7		PPARGC1A	PT K2B	IGFBP3
RICT OR	HBP1	HOXC4	SOD1	PPARG	PT PN1	IKBKB
RPA1	HDAC1	HRAS	JAK2	PPM1D	PT PN11	IL2
S100B	HDAC2	HSF1	JUN	PPP1CA	PYCR1	IL2RG
SDHC	HDAC3	HSP90AA1	JUND	SOD2	RED51	IL6
SERPINE1	HELLS	HSPA1A	KCNA3	SP1	RAD52	IL7
SHC1	T P53	HSPA1B	KL	SPRT N	RAE1	IL7R
SIN3A	T P53BP1	HSPA8	T AF1	SQST M1	VEGFA	INS
T NF	T P63	HSPA9	T BP	SST	WRN	INSR
T OP1	T P73	HSPD1	T CF3	SST R3	XPA	IRS1
T OP2A	T PP2	HT RA2	T ERC	ST AT 3	XRCC5	IRS2
T OP2B	T RAP1	PDGFB	T ERF1	ST AT 5A	XRCC6	CHEK2

T OP3B	T RPV1	PDGFRA	T ERF2	ST AT 5B	YWHAZ	CET P
VCP	T XN	PDGFRB	T ERT	ST K11	ZMPST E24	CISD2
PIK3CB	UBB	PDPK1	T FAP2A	ST UB1	UCP1	CLOCK
CNR1	UBE2I	PIK3CA	T FDP1	SUMO1	UCP2	CLU
COQ7	UCHL1	PEX5	T GFB1	SUN1	UCP3	

Table 1: List of genes of CVD and ageing used in the study.

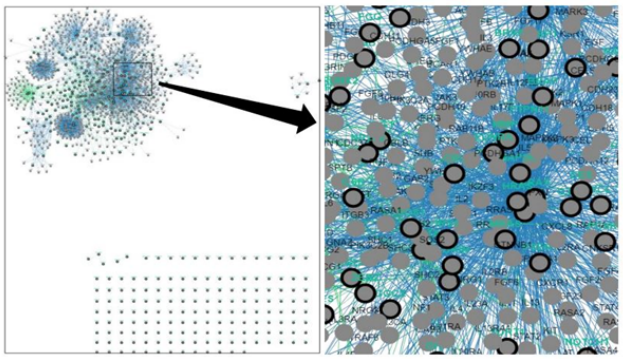

Figure 1: Network of CVD genes complete network including connected and free nodes (grey nodes represent the connected neighborhood genes and nodes with black outline represent the query genes).

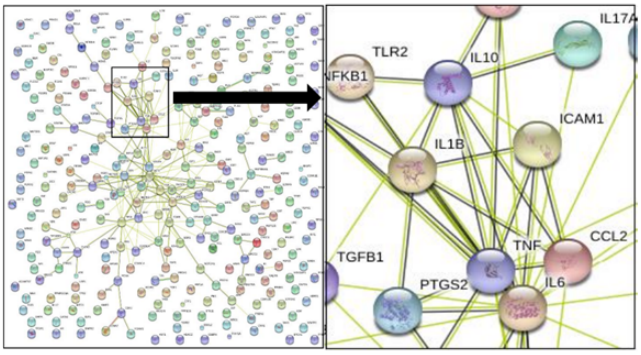

Figure 2: Network created by STRING. Different colour shows different interactions like gene neighbourhood, co-expression, gene fusion, gene co-occurrence and text mining.

pathway, genes involved in it, entries found in the network and information related to reaction. Based on the result, 104 genes which were involved in common pathways of CVD and ageing were taken manually. The network was created for these common genes using STRING. This network shows total 281 nodes in which 132 nodes were connected by 244 edges as shown in Figure 2.

Network created by STRING is analyzed using cytoscape. It allows analyzing the network in terms of betweenness centrality of each node. Betweenness centrality is calculated for every pair of the network and measure of how many times a node is interrupted under the assumption that information primarily flows over the shortest paths between them. Jeong et al. demonstrated the consequence of a single gene deletion in *Saccharomyces cerevisiae* through centrality [13]. The same approach is used to identify the important genes in the network of CVDs and ageing.

As a result, 10 genes are found to be central to the network and are intersecting CVDs and ageing. These are NFKB1, FOXO1, HRAS, SERPINE1, VEGFA, EGFR, IRS1, TNF, PSEN1 and IL6. All these genes are involved in ageing and different CVDs like NFKB1 in Dilated cardiomyopathy, FOXO1 in carotid atherosclerosis, HRAS in congenital heart disease), SERPINE1, VEGFA and EGFR in coronary heart diseases, IRS1 and TNF in myocardial infraction), PSEN1 in Dilated cardiomyopathy and IL6 in peripheral artery disease.

Conclusion

Ageing is the most important risk factor affecting cardiovascular system. Here in this article, we have found out the interaction of ageing and CVDs genes. The study is very important in understanding the mechanism of ageing that increases the prevalence for CVDs. The resultant ten genes are ageing genes and are also reported to be involved in cardiovascular diseases. The ultimate goal of this research is to move towards healthy ageing. It can be achieved by understanding the ageing process to the extent where novel strategies that delay or even prevent the onset of CVDs can be implemented. Developing novel strategies will require a more integrated understanding of the ageing process and wide variety of factors that contributes to CVD risk.

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Conflict of Interest

The authors confirm that they have no conflict of interest.

References

1. Heidenreich PA, Trogdon JG, Khavjou OA, Butler J, Dracup K, et al. (2011) Forecasting the future of cardiovascular disease in the United States: a policy statement from the American Heart Association. Circulation 123: 933-944.
2. North BJ, Sinclair DA (2012) The intersection between aging and cardiovascular disease. Circ Res 110: 1097-1108.
3. Mooney KM, Mc Auley MT (2015) Cardiovascular disease and healthy ageing. J Integr Cardiol 1: 76-78.
4. Costantino S, Paneni F, Cosentino F (2016) Ageing, metabolism and cardiovascular disease. J Physiol 594: 2061-2073.
5. Hamosh A, Scott AF, Amberger J, Bocchini C, Valle D, et al. (2002) Online Mendelian Inheritance in Man (omim), a knowledgebase of human genes and genetic disorders. Nucleic Acids Res 30: 52-55.
6. Roberts RJ (2001) PubMed Central: The GenBank of the published literature. PNAS 98: 381-382.
7. de Magalhaes JP, Toussaint O (2004) GenAge: a genomic and proteomic network map of human ageing. FEBS Lett 571: 243-247.
8. Cerami EG, Gross BE, Demir E, Rodchenkov I, Babur O, et al. (2011) Pathway Commons, a web resource for biological pathway data. Nucleic Acids Res 39: D685-D690.
9. Croft D, O'kelly G, Wu G, Haw R, Gillespie M, et al. (2010) Reactome: a database of reactions, pathways and biological processes. Nucleic Acids Res 39: D691-D697.
10. Szklarczyk D, Franceschini A, Wyder S, Forslund K, Heller D, et al. (2014)

STRING v10: protein-protein interaction networks, integrated over the tree of life. Nucleic Acids Res 43: D447-D452.

11. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, et al. (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13: 2498-2504.
12. Özgür A, Vu T, Erkan G, Radev DR (2008) Identifying gene-disease associations using centrality on a literature mined gene-interaction network. Bioinformatics 24: i277-i285.
13. Jeong H, Mason SP, Barabási AL, Oltvai ZN (2001) Lethality and centrality in protein networks. Nature 411: 41-42.