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Review

Genes involved in premature aging and their association with age-related diseases: A mini review

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ABSTRACT

Aging is an irreversible biological process observed in living organisms, with each cell demonstrating this mechanism. Age-related decline in cellular integrity due to various endogenous and exogenous factors and mechanisms contributes to several diseases based on the site or location of the decline. Cardiovascular diseases, diabetes, cancer, osteoarthritis, and osteoporosis are some examples of age-related diseases. Reports suggest several premature aging genes contribute to the genetic, pathological, and physiological variations of an organism that is similar to the aging organism and might explain the genes associated with aging. We used the DisGeNET web tool to retrieve genes associated with premature aging. We used the Cytoscape software and STRING online tool for identifying protein-protein networks. We retrieved 136 genes associated with premature aging and compared their association with age-related diseases. Many of these premature aging-associated genes were associated with cardiovascular disease (56), diabetes type II (71), Parkinson's disease (54), Alzheimer's disease (86), prostate cancer progression (23), osteoarthritis (15), osteoporosis (53), age-related macular degeneration (35), cataracts (44), and sensorineural hearing loss (26). This article provides a brief review of some of the genes involved in premature aging.

Key words: Ageing, Ageing associated genes, Premature ageing, Premature ageing associated genes

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INTRODUCTION

Aging is a chronological process that is caused by damage to biomolecules, such as DNA, RNA, proteins, and cellular organelles. This damage leads to changes in the functions of cellular organelles, such as the mitochondria, lysosomes, and endoplasmic reticulum. This results in a variety of multicellular functions and age-related diseases that result in death[1–4]. This damage is primarily caused by oxidative DNA stress, which results in single-stranded breaks, double-stranded breaks, and modifications to nitrogen bases or sugar-phosphate backbones[5,6]. Mitochondria are the powerhouse of the cell and generate energy via the electron transport chain (ETC), which releases free radicals, such as O_2^- and H^+, into the inner mitochondrial membrane space and outer mitochondrial space. These radicals damage cellular DNA, RNA, proteins, and mtDNA, thereby damaging the mitochondria, which results in decreased cellular energy production[7]. Lysosomes protect cells by degrading damaged or misfolded proteins and malfunctioning cytoplasmic macromolecules via autophagy. Mutations of lysosomal proteins and enzymes lead to lysosomal malfunctioning, which causes excessive amounts of damaged biomolecules to accumulate inside a cell, causing cell damage[8]. Modifications in rRNA and r-proteins due to oxidative stress leads to ribosomal dysfunction, meaning newly translated proteins may not be able to effectively perform their activities in the cell[9].

The past five decades of research indicate that chronic damage or genetic mutations in some of the genes involved in the aging process leads to physiological and pathological changes that are similar to those seen in the aging process[10]. Bioinformatic tools provide advantages in retrieving enormous amounts of data, while network biology tools can identify associations between genes and proteins. Gene silencing plays a role in inhibiting colon cancer[11]. In this mini-review, we identified 136 genes associated with premature aging using DisGeNET[12], a disease-gene association finding tool, and identified which genes were also associated with other age-related diseases, such as cardiovascular disease, osteoporosis, osteoarthritis, and cataracts. Here, we have briefly reviewed several genes associated with premature aging.

METHODOLOGY

We used the DisGeNET[12] database for finding genes associated with premature aging and age-related diseases and the STRING database[13] and Cytoscape software[14] for identifying protein-protein interactions

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for the genes associated with premature aging. The similarity search was done manually, and relevant articles related to the genes were found using the Google Scholar, Scopus, and PubMed databases.

AGING GENES AND SIMILARITIES

We identified 136 premature aging genes (premature aging syndrome; CUI: C0231341) using DisGeNET. Those with the highest scores were Klotho (*KL*), Werner syndrome gene (*WRN*), excision repair cross complementation group 6 (*ERCC6*), amyloid-beta precursor protein (*APP*), exostosin glycosyltransferase 1 (*EXT1*), lamin A (*LMNA*), RecQ like helicase 3 (*RECQL3/BLM*), RecQ like helicase 4 (*RECQL4*), tumor protein p53 (*TP53*), and Sirtuin 1 (*SIRT1*). When we manually compared the premature aging-associated genes with those associated with age-related diseases, we found several commonalities: 56 of the 1756 cardiovascular disease-associated genes (Cardiovascular Diseases; CUI: C0007222), 71 of the 3134 diabetes type II-associated genes (Diabetes Mellitus, Non-Insulin-Dependent; CUI: C0011860), 54 of the 2078 Parkinson's disease-associated genes (Parkinson Disease; CUI: C0030567), 86 of the 3397 Alzheimer's disease-associated genes (Alzheimer's Disease; CUI: C0002395), 0 of the 166 colorectal cancer-associated genes (Susceptibility to Colorectal Cancer, 12; CUI: C3554460), 23 of the 398 prostate cancer-associated genes (Prostate Cancer Progression; CUI: C1739135), 15 of the 368 osteoarthritis-associated genes (Osteoarthritis, Knee; CUI: C0409959), 53 of the 1098 osteoporosis-associated genes (Osteoporosis; CUI: C0029456), 44 of the 878 cataract-associated genes (Cataract; CUI: C0086543), 35 of the 685 macular degeneration-associated genes (Age-related Macular Degeneration; CUI: C0242383), 26 of the 783 hearing loss-associated genes (Sensorineural Hearing Loss [disorder]; CUI: C0018784)[12]. As colorectal cancer was not associated with any premature aging genes, it has been excluded from **Table 1** (**Table 1** , **Figure 1**).

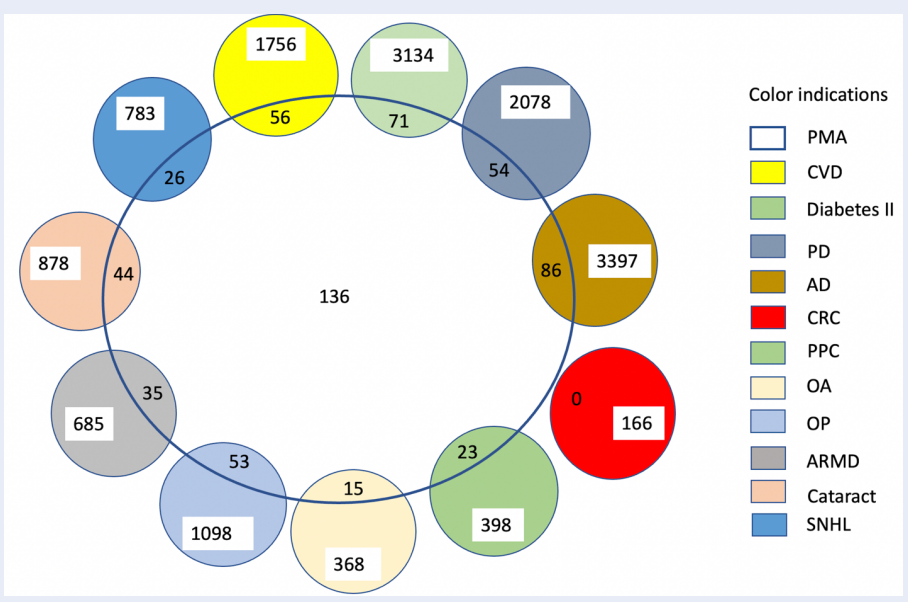

Figure 1: **Indication of the number of similar genes with premature ageing genes**. Various colours indicate various diseases and the number in a square box inside the circle indicates the total number of genes associated with the specific disease and the number inside the white circle indicates the number of similar genes from that specific disease-associated genes.
Abbreviations: **PMA**: Pre-mature ageing genes, **CVD**: Cardiovascular disease, **PD**: Parkinson's disease, **AD**: Alzheimer's disease, **CRC**: Colorectal cancer, **PPC**: Progression of prostate cancer, **OA**: Osteoarthritis, **OP**: Osteoporosis, **ARMD**: Age-related macular degeneration, **SNHL**: Sensory neural hearing loss.

Table 1: Genes associated with premature ageing and the number of similar genes associated with various age-related diseases

S/N	PMA	CVD	DTII	PD	AD	PPC	OA	OP	ARMD	Cataract	SNHL	No.
1.	KL	✓	✓	✓	✓		✓	✓				6
2.	WRN	✓	✓					✓		✓		4
3.	ERCC6							✓	✓	✓	✓	4
4.	APP	✓	✓	✓	✓				✓			5
5.	EXT1		✓					✓				2
6.	LMNA	✓	✓	✓	✓			✓		✓	✓	7
7.	BLM		✓		✓					✓		3
8.	RECQL4							✓		✓		2
9.	TP53	✓	✓	✓	✓	✓	✓	✓	✓	✓		9
10.	SIRT1	✓	✓	✓	✓		✓	✓	✓	✓		8
11.	ZMPSTE24		✓					✓			✓	3
12.	CISD2		✓		✓						✓	3
13.	ATM	✓	✓	✓	✓	✓			✓	✓		7
14.	FGF23	✓	✓	✓	✓			✓				5
15.	HTRA2			✓	✓					✓		3
16.	HSPA9		✓	✓	✓							3
17.	SPRTN											0
18.	ARNTL	✓	✓	✓	✓							4
19.	CDKN2A	✓	✓	✓	✓	✓			✓	✓	✓	8
20.	IGF1	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
21.	CSH1											0
22.	CSH2											0
23.	SOX2		✓	✓	✓	✓				✓	✓	6
24.	ROBO3										✓	1
25.	SOD1	✓	✓	✓	✓			✓	✓	✓		7
26.	BUB1B									✓		1
27.	ANGPTL2	✓	✓		✓			✓	✓			5
28.	VDR	✓	✓	✓	✓	✓	✓	✓				7
29.	BMI1		✓	✓	✓			✓				4
30.	TH tyrosine hydroxylase	✓	✓	✓	✓							4
31.	ELN	✓	✓		✓			✓	✓	✓	✓	7
32.	ERCC8									✓	✓	2
33.	CYP27A1	✓	✓		✓			✓	✓	✓		6
34.	DKC1							✓		✓		2
35.	EMD											0
36.	CDKN1A		✓	✓	✓	✓						4
37.	ERCC2								✓	✓	✓	3
38.	PYCR1							✓				1
39.	SFRP1	✓			✓	✓		✓				4
40.	CHMP1B											0
41.	WRNIP1											0
42.	SOD2	✓	✓	✓	✓			✓	✓	✓	✓	8
43.	SOD3	✓	✓	✓	✓	✓				✓		6
44.	TWNK			✓				✓		✓	✓	4
45.	SNAI2										✓	1

Continued on next page

Table 1 continued

S/N	PMA	CVD	DTII	PD	AD	PPC	OA	OP	ARMD	Cataract	SNHL	No.
46.	PSMD2		✓		✓							2
47.	TNMD		✓	✓	✓				✓	✓		5
48.	RAD51			✓					✓	✓		3
49.	RBBP4											0
50.	BCL2		✓	✓	✓	✓	✓	✓	✓	✓		8
51.	SMURF2							✓				1
52.	SCT	✓										1
53.	SLC3A2											0
54.	SRSF5		✓		✓							2
55.	BRCA1	✓	✓		✓	✓		✓		✓		6
56.	CAT	✓	✓	✓	✓			✓	✓	✓	✓	8
57.	IKBKG									✓		1
58.	CAV1	✓	✓	✓	✓	✓		✓	✓			7
59.	RUNX2		✓			✓	✓	✓			✓	5
60.	TP63	✓		✓	✓						✓	4
61.	BANF1		✓					✓				2
62.	RECQL5											0
63.	ATG5		✓	✓	✓			✓				4
64.	TBPL1	✓			✓				✓			3
65.	CLOCK	✓	✓	✓	✓	✓		✓				6
66.	CUL4A				✓							1
67.	SPNS1											0
68.	CASP2				✓							1
69.	SRF				✓	✓						2
70.	ROPN1L				✓							1
71.	TERC	✓	✓		✓			✓		✓		5
72.	TERF2	✓	✓		✓				✓			4
73.	TFAM		✓	✓	✓							3
74.	TOP3A										✓	1
75.	C3 complement C3	✓	✓		✓				✓			4
76.	VCP			✓	✓					✓		3
77.	XPO1											0
78.	EDS8											0
79.	NCOR2		✓									1
80.	MAPK1	✓	✓	✓	✓			✓	✓		✓	7
81.	CFDP1	✓			✓							2
82.	EFEMP1						✓		✓			2
83.	FGF1		✓	✓	✓							3
84.	SIRT2	✓	✓	✓	✓			✓				5
85.	FOXO3	✓	✓	✓	✓	✓		✓				6
86.	EXOSC2										✓	1
87.	COMMD3-BMI1		✓					✓				2
88.	KCNH4				✓							1
89.	FUS			✓	✓							2
90.	G6PD	✓	✓	✓	✓				✓	✓		6
91.	ASPM				✓				✓			2
92.	IS1	✓										1

Continued on next page

Table 1 continued

S/N	PMA	CVD	DTII	PD	AD	PPC	OA	OP	ARMD	Cataract	SNHL	No.
93.	COPD	✓	✓					✓		✓		4
94.	ERCC4									✓	✓	2
95.	ERCC3	✓							✓	✓	✓	4
96.	PPARGC1A	✓	✓	✓	✓			✓	✓	✓		7
97.	TUSC2			✓								1
98.	H3P10					✓						1
99.	ADCYAP1		✓	✓	✓		✓				✓	5
100	KCNH8				✓							1
101	CYLD			✓	✓					✓		3
102	DPP4	✓	✓	✓	✓			✓				5
103	AGTR2	✓	✓		✓							3
104	EIF4G2	✓	✓		✓							3
105	TMEM201				✓							1
106	ELK1											0
107	EPHB2		✓	✓	✓			✓				4
108	SENP6											0
109	GLO1		✓		✓			✓				3
110	ASPA				✓							1
111	MUC1	✓			✓			✓				3
112	MYOD1	✓										1
113	NFE2L2	✓	✓	✓	✓	✓		✓	✓	✓		8
114	SERPINE1	✓	✓	✓	✓		✓	✓	✓	✓		8
115	GEMIN4				✓					✓		2
116	FOXP3	✓	✓		✓		✓					4
117	SIRT6	✓	✓	✓	✓							4
118	PIN1	✓	✓	✓	✓							4
119	POLG			✓	✓			✓		✓	✓	5
120	APTX											0
121	ENOSF1											0
122	ASIP		✓	✓	✓							3
123	MMP9	✓	✓	✓	✓	✓	✓	✓	✓	✓		9
124	GUSB				✓							1
125	A1CF				✓							1
126	H1-4											0
127	APOE	✓	✓	✓	✓			✓	✓	✓	✓	8
128	IGFBP3	✓	✓		✓							3
129	IL1A	✓	✓	✓	✓	✓	✓	✓	✓			8
130	IL1B	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	10
131	AR	✓	✓	✓	✓	✓	✓	✓				7
132	LBR				✓							1
133	LPA	✓	✓	✓	✓				✓			5
134	MDM2	✓	✓			✓			✓			4
135	MECP2				✓			✓				2
136	NHP2							✓		✓		2
Total number of similar genes out of 136 PMA genes		56	71	54	86	23	15	53	35	44	26	

Abbreviations: **PMA**: Pre-mature ageing genes, **CVD**: Cardiovascular disease, **DTII**: Diabetes type II, **PD**: Parkinson's disease, **AD**: Alzheimer's disease, **CRC**: Colorectal cancer, **PPC**: Progression of prostate cancer, **OA**: Osteoarthritis, **OP**: Osteoporosis, **ARMD**: Age-related macular degeneration, **SNHL**: Sensory neural hearing loss, **No.**: Number of age-related diseases the genes are present

The genes were selected from DisGeNET by entering the name of the disease (*i.e.*, premature aging). Then, we used the DisGeNET Cytoscape App, which is an application designed for visualizing, querying, and analyzing DisGeNET data. Through a variety of built-in features, the application helps users understand genetics and explore complex human diseases and enables easy generation of disease-gene, disease-variant networks, disease-disease, and gene-gene networks. Nodes are connected if they share a neighbor in the original gene-disease network. These networks can be built around specific genes and diseases or based on the source or disease class[12]. For the gene network analysis of the 136 genes associated with premature aging, we found 133 nodes and 822 edges. The average node degree was 12.4, and the average local clustering coefficient was 0.512 based on the results of the STRING online network analysis tool and Cytoscape software (**Figure 2** and **Figure 3**, respectively)[13,14].

Klotho *(KL)*

In early 1997, Kuro-o *et al.* reported that mutations in the *KL* gene in mice led to a syndrome that resembled aging. Mice with the aging phenotype showed growth retardation, short life spans, and atrophy of the testes, uterus, ovaries, and thymus. In the aorta and middle-sized muscular arteries, medial calcification and intimal thickening were observed. The small renal arteries also showed extensive calcification and arteriosclerosis, and ectopic calcification was found in various organs, such as the arterial walls of the stomach, bronchial mucosa, alveolar cells, choroid plexuses, skin, testes, and cardiac muscle. There was a decrease in bone mineral density and the appearance of sparse hair, emphysema, and abnormalities in growth hormone (GH), luteinizing hormone, and follicle-stimulating hormone-producing cells in the pituitary gland. Increased calcium and phosphorus levels were observed, and hypoglycaemic conditions developed due to decreased pancreatic insulin levels. Further, PBMC analysis showed that the lymphocyte-to-leukocyte ratio decreased while total protein, albumin, cholesterol, and triglyceride levels were normal. In control mice, the *KL* gene was highly expressed in the brain, pituitary glands, skeletal muscle, kidney, urinary bladder, pancreas, testis, and ovaries and slightly expressed in the placenta, aorta, colon, and thyroid gland. The *KL* gene was downregulated in the brain and kidney of mice with mutated *KL* genes[10]. Wang *et al.* reported that *KL* gene transfer to rat aorta smooth muscle (RASM) cells attenuated superoxide production and oxidative stress by suppressing Nox2 NADPH oxidase protein expression. This decreased angiotensin II(AngII)-induced superoxide production, oxidative damage, and circumvented apoptosis. However, intracellular cAMP levels and PKA activity increased in a dose-dependent manner in RASM cells[15].

Werner syndrome gene (*WRN*)

WRN gene, also known as Werner syndrome RecQ-like helicase (*WRN/RECQL2*), plays major roles in genomic stability maintenance, DNA repair, replication and transcription, and telomere maintenance. Defects in this gene cause Werner syndrome, which is characterized by faster aging and higher rates of cancers (**https://www.ncbi.nlm.nih.gov/gene/7486#gene-expression).** In a recent study, Zimmer *et al.* reported that mutations in the *WRN* gene were found in 80 cancer primary tumor samples out of 6854 samples (1.2 %), with mutations being more prevalent in right-sided tumors. Tumor mutational burden (TMB), programmed death-ligand 1(PD-L1), and microsatellite instability-high/mismatch repair system deficient (MSI-H/dMMR) biomarkers were higher in the *WRN*-mutated group than the *WRN*-wild type group. TP53, KRAS, and APC were found in 47 (71%), 34 (49%), and 56 (73%) samples, respectively, in the *WRN*-mutated and *WRN* wild-type groups[16].

Excision repair cross-complementation group 6 (*ERCC6*)

ERCC6 is also referred to as ERCC excision repair 6, chromatin remodeling factor/Cockayne syndrome B protein, and has been reported to be involved in DNA repair mechanisms via the nucleotide excision repair (NER) pathway. It has been reported to correct a NER defect in UV-sensitive Chinese hamster ovary (CHO) mutants. The same group also investigated Cockayne syndrome using Cellosaurus cell lines (CS1AN) with mutations in the *ERCC6I* gene[17,18]. The *ERCC6* gene was transfected to the mutants, and more UV-surviving colonies were observed than the heterogeneous colonies found in CS1AN. This indicated that *ERCC6* correction occurred in the mutant cells.

Amyloid-beta precursor protein (*APP*)

APP is located on chromosome 21q21 and encodes a ubiquitously expressed type 1 transmembrane protein. *APP* generally undergoes non-amyloidogenic processing by consecutive cleavage through alpha and

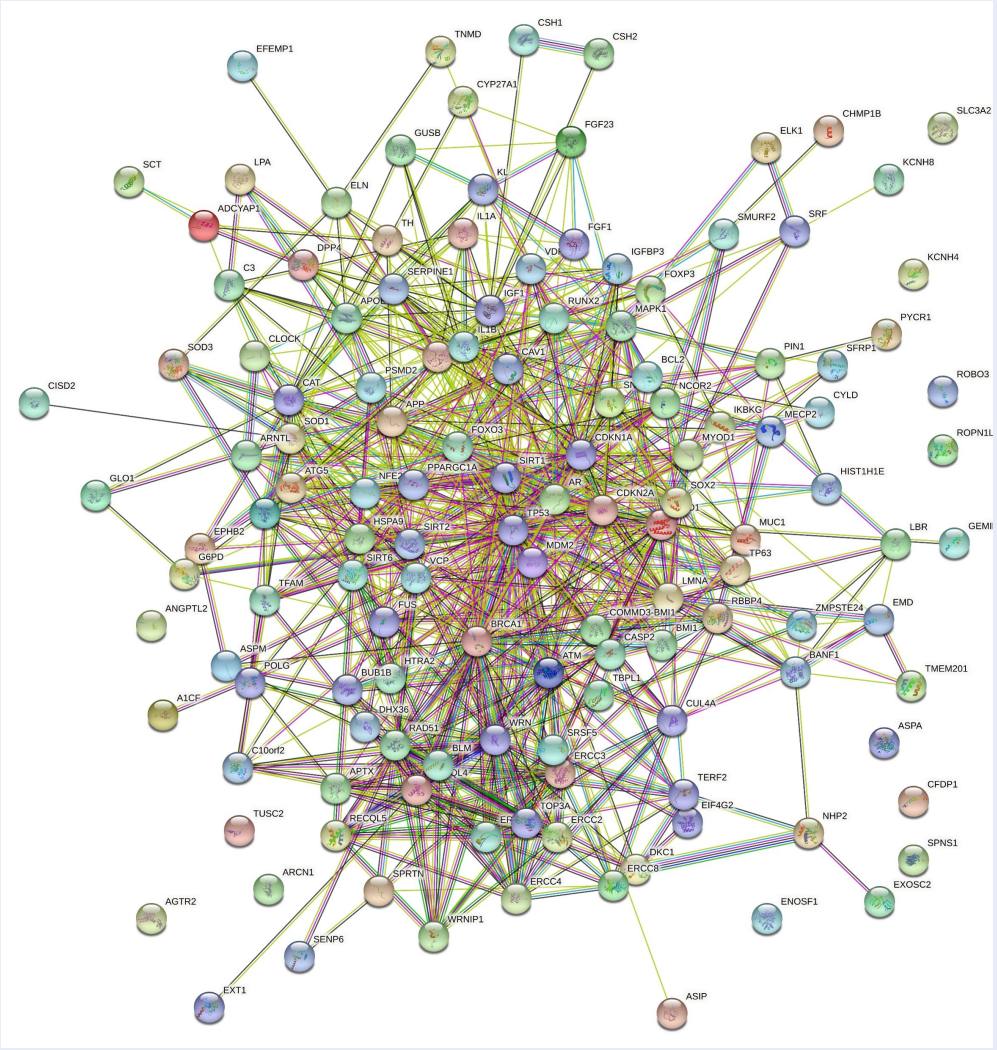

Figure 2: Protein-Protein Interaction that is associated with Pre-mature ageing plotted with STRING database online tool.

gamma secretases within the Aβ domain. This leads to non-pathogenic fragments, sAPP- fragments, and C-terminal fragments (CTFs). *APP* can be subjected to sequential proteolytic cleavage by beta and gamma secretases, which results in neurotoxic Aβ peptides (sAPP- and CTF)[19]. Muche *et al.* reported that oxidative stress increases the upregulation of *APP* and sAPP-β, induces VEGF synthesis, and nitric oxide oxygen free radical production. It also induces a variety of changes in endothelial phospo-p42/44 MAPK expression, which indicates that oxidative stress might play a major role in the regulation of the beta site *APP* cleavage enzyme-1 (BACE)[20].

Exostosin glycosyltransferase 1 (*EXT1*)

EXT1 encodes an endoplasmic reticulum-resident type II transmembrane glycosyltransferase known to be involved in the chain elongation step of heparan sulfate biosynthesis (**https://www.ncbi.nlm.nih.gov/gene/2131**). *EXT* is genetically heterogeneous. *EXT1* is located on chromosome 8q23-q24, *EXT2* on chromosome 11p11-p12, and *EXT3* on the short arm of chromosome 19. *EXT1* is highly expressed, encodes a 746 amino acid residue protein, and possesses a tumor suppressor function. Reports have indicated that *EXT1* mutations are present in chondrosarcoma[21].

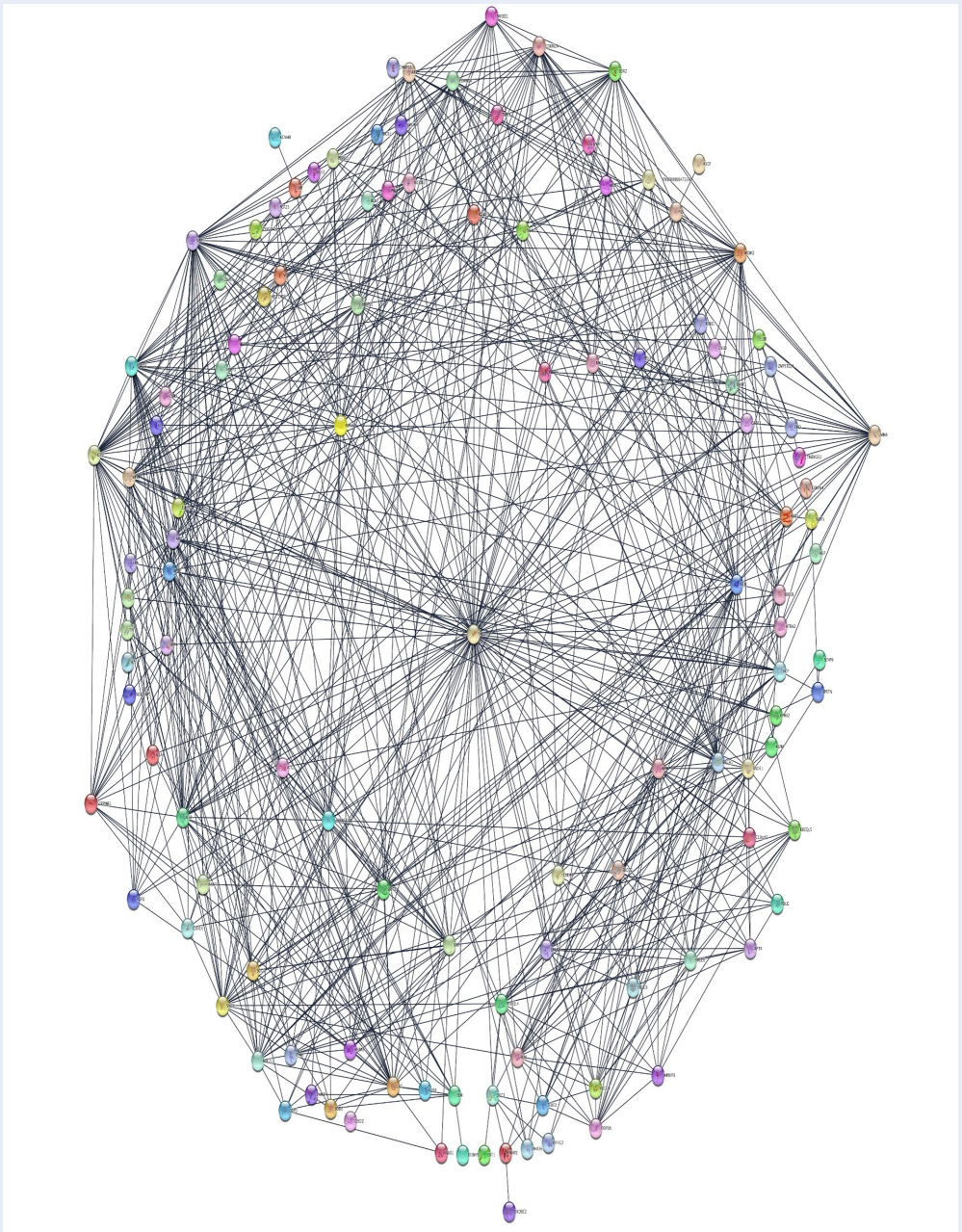

Figure 3: **Protein-Protein Interaction obtained from Cytoscape software.**

Lamin A (LMNA)

The *LMNA* gene encodes lamin A, lamin C, lamin C2, and lamin A delta 10 and is expressed in most tissues. Reports indicate that mutations in lamina/nuclear envelope proteins cause genetic diseases, such as laminopathies. Researchers have identified over 400 mutations in *LMNA* are responsible for diseases[22]. Lamin expression is reported to be regulated by the tumor suppressor p53 and retinoblastoma protein (pRb), telomere functions, regulators of the cell cycle, apoptosis, replicative senescence, and autophagy. Reports also suggest that mutant progerin lamin A, which causes Hutchinson-Gilford Progeria Syndrome (HGPS), is upregulated during normal aging[23,24]. Sieprath *et al.* reported that the oxidation of conserved cysteine residues in the tail domain of lamin A by oxidative stress appears to impact its function and promote cellular senescence and susceptibility to reactive oxygen species (ROS). Furthermore, increased telomere shortening has been observed in most human fibroblast cell lines expressing various mutant LMNA variants. Previous studies indicate that upregulation of wild-type LMNA also causes increased telomere shortening. In laminopathies, ROS are linked to DNA damage[25].

RecQ-like helicase 3 (*RECQL3/BLM*)

BLM or *RECQL3* is an ATP-dependent RECQ DNA helicase that plays a pivotal role in the regulation of DNA replication, recombination, and homologous and non-homologous double-stranded break repair (DSBR). Mutations in *BLM* cause an autosomal recessive disorder known as Bloom syndrome (BS) that is characterized by genomic instability, premature aging, increased susceptibility to cancer, and immunodeficiency. *BLM* is located on chromosome 15q26.1 and encodes a 1417 amino acid protein-coding gene. *BLM* levels are higher during the S and G2 phases of the cell cycle[26]. Subramanian *et al.* reported that *BLM*-deficient cells collected from BS patients exhibited higher mitochondrial mass, increased mitochondrial transcription factor A (TFAM) levels, higher ATP levels, and increased respiratory reverse capacity. Increased levels of ROS and DNA base damage and an oxidative stress-dependent DNA replication rate reduction were also reported[27].

RecQ like helicase 4 (*RECQL4*)

RECQL4 is a DNA helicase that belongs to the RecQ helicase family, which consists of other helicases, such as *RECQL2* (*WRN*) and *RECQL3* (*BLM*). RecQ helicases play major roles in DNA unwinding, replication, transcription, and repair. Reports indicate that mutations in these genes lead to BS, Werner syndrome, and Rothmund-Thomson syndrome (RTS) and are associated with premature aging and increased cancer prevalence[28,29]. A study by Werner *et al.* on fibroblasts collected from RTS patients found that in normal human fibroblasts, *RECQL4* was localized to the cytoplasm, with nuclear translocation and foci formation occurring in response to oxidant stimulation, while RTS fibroblasts exhibited irreversible growth arrest. RTS cells that are exposed to oxidative stress demonstrated decreased DNA synthesis, indicating that *RECQL4*-deficient fibroblasts were more sensitive to oxidants[30].

Tumor protein p53 (*TP53*)

TP53 acts as a tumor suppressor and encodes the p53 transcription factor, a prominent tumor suppressor and regulator of different signaling pathways. P53 plays important roles in cell cycle arrest, DNA repair, cellular senescence, and apoptosis. *TP53* mutations have been detected in most cancer types at varying prevalences, such as in 10% of hematopoietic malignancies to around 100% of high-grade serous ovarian carcinomas[31].

Sirtuin 1 (*SIRT1*)

SIRT1 is a mammalian nicotinamide adenine dinucleotide (NAD+)0dependent histone deacetylase that acts as an epigenetic mediator of longevity, regulates DNA stability, and protects cells from oxidative stress. *SIRT1* has been reported to be expressed in the brain, liver, heart, spleen, kidney, skeletal muscle, endothelial tissue, and pancreas. The expression and activation of *SIRT1* leads to the modulation of its downstream pathways via targeting of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), peroxisome proliferators-activated receptor-gamma (PPAR-γ), protein tyrosine phosphatase (PTP), forkhead transcriptional factors (FoxO subgroup), adenosine monophosphate-activated protein kinase (AMPK), CRE-binding protein regulated transcription coactivator 2 (CRTC2), endothelial nitric oxide synthase (eNOS), p53, myogenic differentiation (MyoD), liver X receptor (LXR), and transcription factor E2F1[32]. Liver *SIRT1* levels decrease with age, which is associated with simultaneously increased DNA damage. A similar trend has been reported in the arteries, indicating *SIRT1*'s association with cardiovascular diseases[33].

PATHWAY ANALYSIS

We conducted the pathway analysis of the identified genes using the KEGG software. The genes entered were *KL*, *WRN*, *ERCC6*, *APP*, *EXT1*, *LMNA*, *RECQL3/BLM*, *RECQL4*, *TP53*, and *SIRT1*. We obtained pathways for 8 of the genes[34–36]. The entry identities of these genes are given below.

1. klotho (entry id: map04211, Longevity regulating pathway)
2. Werner syndrome gene (WRN): No data on KEGG database
3. ERCC6 *(*entry id: map03420, Nucleotide excision repair*)*
4. APP (entry id: map04064 (NF-kappa B signaling pathway), *(*entry id: map04668 (TNF signaling pathway), entry id: map05010 (Alzheimer disease)
5. Lamin A ((entry id: map04210 (Apoptosis), *(*entry id: map05410 (Hypertrophic cardiomyopathy), entry id: map05412 (Arrhythmogenic right ventricular cardiomyopathy), entry id: map05414 (Dilated cardiomyopathy)
6. RecQ-like helicase 3 (RECQL3/ BLM): Homologous recombination
7. RecQ like helicase 4 (*RECQL4*): No data on KEGG database
8. TP53: Cellular senescence (map04218): Longevity regulating pathway (map04211): Cell cycle (map04110): Apoptosis (map04210)
9. SIRT1: Longevity regulating pathway (map04211), Cellular senescence (map04218), Glucagon signaling pathway (map04922), Metabolic pathway(map01100)

The results obtained from KEGG database for the different ageing or ageing related disease pathway for these genes are given in **Supplement**.

DISCUSSION

Aging is related to the type of oxidative stress an individual is exposed to. Oxidative stress plays an important role in the early aging phenotype, and low-dose chronic exposure to oxidants plays an important role in many diseases, particularly cancer. In vitro studies indicate that when cells are exposed to stress conditions, they either attenuate the stress or adapt to the stress condition. Ghosh et al. reported that NADH dehydrogenase subunits are overexpressed following chronic exposure to the oxidant H_2O_2[37]. Chronic low-dose exposure to H_2O_2 enhances the activity of antioxidant enzymes, such as catalase and superoxide dismutase[38]. The same group investigated -radiation-induced damage and found that prolonged treatment enhanced HPRT mutations in V79 cells compared to parental cells. Furthermore, conditioned cells also showed higher numbers of radiation-induced mutations[39,40]. Oxidative stress has been associated with cellular senescence and colon cancer[41]. When cellular stress exceeds cell limits, it leads to cellular biomolecule damage. The use of antioxidants can neutralize cellular oxidants and alleviate various cellular stress-associated diseases[42]. Naturally occurring molecules that have antioxidant properties, such as vitamin C, vitamin E, and polyphenols *(e.g.*, flavonols and flavanones), can be used as antioxidants to alleviate oxidative stress and neutralize oxidants[43]. Nanotechnology is an advanced technology that can increase the efficiency of drug delivery and drug bioavailability. Agraharam *et al.* reported that nanoencapsulation of a flavonol (Myricetin) led to increased bioavailability and enhanced antioxidant and antioxidant enzyme properties, such as catalase, glutathione peroxidase, and superoxide dismutase[44].

To prevent replicative senescence or genomic instability, various factors are located at telomeres to regulate their length, structure, and function. There are several rare heterogeneous premature-aging diseases caused by Mendelian defects in these factors, which are known as short-telomere syndromes, telomeropathies, or telomere biology disorders (TBDs). The main functions associated with TBD-causing genes identified have been described by researchers. Studies have explored how TBDs are influenced by molecular mechanisms, including genetic anticipations, phenocopies, incomplete penetrance, and somatic genetic rescues. Studies have also discussed the diagnostic, therapeutic, and clinical implications of TBD phenotypic and genetic features, as well as the biological aspects of human telomeres, aging, and cancer[45]. The process of aging is complex and multifaceted. It results in the widespread functional decline of all organs and tissues; however, it is unclear whether aging is a result of a unifying cause or multiple factors. A wide range of molecular, cellular, and physiological characteristics are associated with the aging process phenotypically, such as genomic and epigenomic changes, proteostasis loss, deterioration of cell and subcellular functions, and deregulation of signaling pathways. The range of characteristics associated with this have resulted in a lack of clarity regarding their relative importance, mechanistic interrelationships, and hierarchical order. In recent years, researchers have accumulated evidence suggesting that DNA damage is responsible for most,

if not all, aspects of aging. A unified approach to counteracting age-related dysfunction and disease may be achieved by improving the current understanding of DNA damage and its mechanistic relationships with aging[46]. There has been much discussion and improved understanding regarding how epigenetic changes occur during the aging process and how epigenetic mechanisms impact health and lifespan extension. The paper outlines questions for future research on interventions designed to rejuvenate the epigenome and delay the aging process[47]. Some natural compounds have been found to attenuate the aging process. *Xylopia aromatica, Xylopia sericea,* and other organisms contain a natural substance called myrtenal, which possesses oxidative stress-scavenging properties. In diabetic rats, myrtenal has reduced oxidative stress[48].

In the present study, we identified 136 genes that are associated with different age-related diseases. Of the 136 genes, 9 had high scores in relation to their association with premature aging. This review explained the roles of these genes in aging and aging-related diseases. The present work is an in silico study. Therefore, experiments related to the expression of these genes should be undertaken and validated using various models of aging.

CONCLUSION

The premature aging genes that were retrieved from DisGeNET played important roles in maintaining cellular integrity, DNA repair, cell cycle regulation, cellular stress regulation, and tumor suppression pathways. The presented data indicate that mutations or age-related damage to these genes at specific sites results in age-related diseases, such as cardiovascular disease, diabetes, cancer, osteoarthritis, and osteoporosis. The data also suggests that age-related diseases are associated with aging-associated genes, and earlier genetic diagnosis may enable early treatment.

ABBREVIATIONS

AD: Alzheimer's disease
AMPK: adenosine monophosphate activated protein kinase
AngII: angiotensin II
ARMD: Age-related macular degeneration
Aβ peptides: Amyloid beta
BS: Bloom syndrome
cAMP: Cyclic Adenosine monophosphate
CHO: Chinese hamster ovary
CRC: Colorectal cancer
CRTC2: CRE-binding protein regulated transcription coactivator 2
CS1AN: Cellosaurus cell lines
CTFs: C-terminal fragments
CVD: Cardiovascular disease
dMMR: mismatch repair system deficient
DNA: Deoxyribonucleic acid
DSBR: double-strand break repair
eNOS: endothelial nitric oxide synthase
ETC: Electron transport chain
GH: Growth hormone
H_2O_2: Hydrogen peroxide
HGPS: Hutchinson-Gilford Progeria Syndrome
LXR: liver X receptor
MAPK: Mitogen-activated protein kinase
MSI-H: microsatellite instability-high
mtDNA: Mitochondrial DNA
MyoD: myogenic differentiation
NADH: Nicotinamide adenine dinucleotide (NAD) + hydrogen (H)
NER: Nucleotide Excision Repair
NF-κB: nuclear factor kappa Beta
OA: Osteoarthritis
OP: Osteoporosis
PBMC: Peripheral blood mononuclear cell
PD: Parkinson's disease
PD-L1: programmed death-ligand 1
PGC-1α: Coactivator peroxisome proliferator-activated receptor gamma coactivator 1-alpha
PKA: Protein kinase A
PMA: Pre-mature ageing genes
PPAR-γ: Peroxisome proliferators-activated receptor-gamma
PTP: Protein tyrosine phosphatase
RASM: rat aorta smooth muscle
RNA: Ribonucleic acid
ROS: reactive oxygen species
r-Proteins: Ribosomal Proteins
rRNA: Ribosomal RNA
RTS: Rothmund-Thomson syndromes
sAPP-$\propto$: soluble Amyloid precursor protein - $\propto$
sAPP-β: soluble Amyloid precursor protein - β
SNHL: Sensory neural hearing loss
TFAM: Mitochondrial transcription factor A
TMB: Tumor mutational burden
V79 cells: Chinese hamster cells
VEGF: Vascular endothelial growth factor

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The authors declare that they have no competing interests.

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