Systematic analysis of the gerontome reveals links between aging and age-related diseases

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Supplementary Material

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Supplementary Tables

Table S1 - Functional annotation of CAD-genes - aging or diseases genes

Terms Categories	Terms Summary	E. Score
Aging / All diseases classes		
GOTERM_BP_FAT	Negative regulation of apoptosis, cell death.	9.29
GOTERM_BP_FAT	Positive regulation of apoptosis, cell death, DNA damage response.	4.74
GOTERM_CC_FAT UP_SEQ_FEATURE GOTERM_MF_FAT SP_PIR_KEYWORDS	Lumen, DNA binding, nucleus.	4.54
GOTERM_BP_FAT SP_PIR_KEYWORDS	Cell Cycle.	4.25
GOTERM_BP_FAT GOTERM_CC_FAT SP_PIR_KEYWORDS	DNA repair, DNA damage, response to stress, nucleoplasm.	4.24
GOTERM_BP_FAT	Response to stimulus, response to hormones.	4.03
KEGG_PATHWAYS	Cancer.	3.84
GOTERM_BP_FAT	Response to UV radiation.	3.78
GOTERM_BP_FAT GOTERM_MF_FAT SP_PIR_KEYWORDS	Positive regulation of biosynthetic process, positive regulation of metabolic process, regulation of transcription.	3.60
GOTERM_BP_FAT	Positive regulation of DNA metabolic process, positive regulation of DNA replication.	3.12
GOTERM_BP_FAT	Positive regulation of protein metabolic process, positive regulation of phosphorylation, positive regulation of kinases cascade.	3.11
GOTERM_BP_FAT	& Positive regulation of cell motion, positive regulation of carbohydrates.	2.99
GOTERM_BP_FAT	DNA catabolic process.	2.96
GOTERM_BP_FAT	Response to hormonal stimulus.	2.91
GOTERM_BP_FAT	Apoptosis, cell death.	2.89
GOTERM_BP_FAT	Response to oxidative stress	2.56
GOTERM_BP_FAT	Protein complex.	2.55
GOTERM_BP_FAT	Neuronal development, neuronal differentiation	2.52
Aging / Neoplasms		
GOTERM_BP_FAT	Negative regulation of apoptosis, cell death.	5.80
SP_PIR_KEYWORDS GOTERM_BP_FAT GOTERM_MF_FAT GOTERM_CC_FAT	DNA repair, DNA damage, DNA binding, nucleoplasm.	4.38
GOTERM_BP_FAT	Regulation of cell cycle.	3.93
SP_PIR_KEYWORDS GOTERM_BP_FAT	Tumor suppressor.	3.51
KEGG_PATHWAYS	Cancer.	3.20
GOTERM_CC_FAT	Nucleoplasm.	2.60

Aging / Nutritional and Metabolic diseases		
GOTERM_BP_FAT	Response to insulin stimulus.	3.45
GOTERM_BP_FAT	Positive regulation of lipid metabolic process.	2.51
Aging / Musculoskeletal diseases		
SP_PIR_KEYWORDS GOTERM_CC_FAT	Secreted, extracellular region.	3.10
Aging / Eye diseases		
GOTERM_BP_FAT	Positive regulation of RNA metabolic process.	2.93

E.Score - Enrichment Score

Table S2 - Number of connections analysis for CAD-genes - per class and disease

Class/Disease	Median of CAD-genes	Median of Aging or Disease Genes	MW
Per Class			
All Classes	**47**	11	**<0.001**
Cardiovascular	29	17	0.438
Eye	47	37	0.606
Immune System	8.5	**43**	**0.047**
Musculoskeletal	14.5	37	0.107
Neoplasms	**47**	23.5	**0.001**
Nervous System	45	30	0.398
Nutritional and Metabolic diseases	30.5	19	0.324
Respiratory Tract	39	32	0.136
Per Disease			
Adenocarcinoma	71.5	40	0.183
Alzheimer's Disease	46	36	0.324
Arteriosclerosis	22.5	44.5	0.123
Arthritis	29.5	38.5	0.949
Asthma	27	34	0.519
Atherosclerosis	3	**46**	**0.002**
Autoimmune disease	39	47	0.847
Breast Neoplasm	**49**	37	**0.020**
Colorectal Neoplasm	50.5	40	0.520
Coronary Disease	35.5	32	0.805
Diabetes Mellitus, type 1	12.5	37	0.106
Diabetes Mellitus, type 2	29	25	0.908
Hypersensitivity	2	**46**	**0.019**
Hypertension	28	27	0.231
Lung Neoplasm	47	37	0.354
Multiple Sclerosis	43	45	0.340
Myocardial Infarction	27	30	0.720
Obesity	35.5	37	0.375
Osteoporosis	6	**47**	**0.039**
Parkinson's Disease	34.5	45	0.227
Prostatic Neoplasm	27	42	0.847
Stomach Neoplasm	27	42	0.833

MW - p-value from Mann-Whitney U test

Table S3 - Functional annotation of non-overlapping genes - genome

Terms Categories	Terms Summary	E. Score
Aging / All diseases classes		
GOTERM_BP_FAT	Response to DNA damage stimulus, DNA metabolic process, DNA repair.	22.70
GOTERM_CC_FAT SP_PIR_KEYWORDS GOTERM_MF_FAT GOTERM_BP_FAT	Nucleus, lumen, regulation of transcription.	19.37
GOTERM_BP_FAT SP_PIR_KEYWORDS	Negative regulation of apoptosis, positive regulation of apoptosis, cell death.	14.02
GOTERM_BP_FAT SP_PIR_KEYWORDS GOTERM_MF_FAT GOTERM_CC_FAT	Positive regulation of biosynthetic process, positive regulation of gene expression, positive regulation of transcription, DNA binding.	13.91
GOTERM_BP_FAT	Activation of receptor protein signalling pathway.	10.06
GOTERM_MF_FAT	Protein dimerization.	9.56
GOTERM_BP_FAT	Response to radiation, UV.	9.45
SP_PIR_KEYWORDS GOTERM_BP_FAT UP_SEQ_FEATURE INTERPRO GOTERM_MF_FAT SMART	ATP-binding, protein phosphorylation, Serine/threonine protein kinase.	8.18
GOTERM_BP_FAT BIOCARTA	Response to hormone stimulus, response to insulin stimulus, PTEN dependent cell cycle arrest and apoptosis.	7.96
GOTERM_BP_FAT GOTERM_MF_FAT	Negative regulation of cellular biosynthetic process, negative regulation of transcription.	7.73
GOTERM_CC_FAT	Nuclear chromatin.	7.70
GOTERM_BP_FAT	Positive regulation of multicellular organism growth.	5.53
KEGG_PATHWAYS UP_SEQ_FEATURE INTERPRO GOTERM_MF_FAT	Insulin signalling pathway, cancer, type II Diabetes Mellitus, MAP kinase activity, apoptosis.	5.33
GOTERM_BP_FAT SP_PIR_KEYWORDS	DNA repair, DNA recombination, DNA damage.	5.33
GOTERM_BP_FAT	Cell cycle checkpoint.	5.29
GOTERM_BP_FAT	Response to oxidative stress.	5.22
GOTERM_MF_FAT	Transcription cofactor activity.	5.04
GOTERM_BP_FAT	Aging, response to extracellular stimulus.	4.97
GOTERM_BP_FAT SP_PIR_KEYWORDS	Regulation of mitotic cell cycle, interphase.	4.81
GOTERM_CC_FAT GOTERM_MF_FAT GOTERM_BP_FAT SP_PIR_KEYWORDS KEGG_PATHWAYS BIOCARTA	Telomere maintenance, negative regulation of DNA replication, positive regulation of DNA metabolic process.	4.60

GOTERM_BP_FAT	Positive regulation of protein kinase activity, positive regulation of transferase activity, MAPKKK cascade.	4.40
GOTERM_BP_FAT	Transcription.	4.38
GOTERM_BP_FAT	Response to drug, response to bacterium, response to mechanical stimulus.	3.70
GOTERM_BP_FAT	Regulation of cytokine production.	3.58
GOTERM_BP_FAT GOTERM_MF_FAT INTERPRO GOTERM_CC_FAT PIR_SUPERFAMILY COG_ONTOLOGY	Negative regulation of gene expression, histone deacetylase activity, chromatin modification, negative regulation of cell cycle.	3.57
GOTERM_BP_FAT	Regulation of protein binding	3.49
UP_SEQ_FEATURE INTERPRO SMART GOTERM_MF_FAT GOTERM_BP_FAT BIOCARTA	Transmembrane receptor protein serine/threonine kinase signaling pathway.	3.40
GOTERM_BP_FAT SP_PIR_KEYWORDS	Base-excision repair, DNA replication.	3.39
GOTERM_BP_FAT	*in utero* embryonic development.	3.38
KEGG_PATHWAY BIOCARTA BBID	Cancer, Insulin signalling pathway, PTEN dependent cell cycle arrest and apoptosis.	3.35
GOTERM_BP_FAT UP_SEQ_FEATURE INTERPRO GOTERM_MF_FAT	Negative regulation of gene expression, NAD binding.	3.29
GOTERM_BP_FAT	Induction of apoptosis by extracellular signals.	3.19
GOTERM_BP_FAT	DNA geometric change.	3.13
GOTERM_BP_FAT	Macromolecular complex assembly.	3.07
SP_PIR_KEYWORDS GOTERM_MF_FAT PIR_SUPERFAMILY KEGG_PATHWAYS INTERPRO UP_SEQ_FEATURE SMART BIOCARTA	Serine/threonine-protein kinase, MAP kinase activity, SAP kinase activity, BCR signalling pathway.	3.03
GOTERM_BP_FAT	Regulation of homeostatic process, female sex differentiation, positive regulation of myeloid cell differentiation, T cell homeostasis.	2.97
GOTERM_BP_FAT	Negative regulation of protein modification process, regulation of membrane potential.	2.96
GOTERM_BP_FAT	Reproductive process in a multicellular organism, reproductive developmental process, sexual reproduction.	2.95

GOTERM_BP_FAT KEGG_PATHWAY	Negative regulation of binding, regulation of transcription factor activity.	2.79
GOTERM_BP_FAT	Negative regulation of neuron apoptosis, cellular chemical homeostasis, regulation of membrane potential.	2.75
GOTERM_BP_FAT GOTERM_MF_FAT SP_PIR_KEYWORDS	DNA topoisomerase activity, DNA topological change.	2.75
KEGG_PATHWAY BIOCARTA GOTERM_BP_FAT	Signalling pathways (ErbB, TPO, IL 2, MAPKinase, Insulin, EGF, IL 3, BCR, IL 6), epidermal growth factor receptor signaling pathway.	2.75
UP_SEQ_FEATURE INTERPRO SMART	PIK-related kinase.	2.70
GOTERM_BP_FAT	Insulin receptor signalling pathway, regulation of glucose transport.	2.66
GOTERM_BP_FAT	Positive regulation of multicellular organism growth.	2.65
GOTERM_BP_FAT	Regulation of JNK cascade, regulation of stress-activated protein kinase signaling pathway.	2.62
GOTERM_BP_FAT KEGG_PATHWAY BIOCARTA	Insulin receptor signalling pathway, Trka receptor signalling pathway.	2.57
GOTERM_BP_FAT	Regulation of mitochondrial membrane potential, regulation of mitochondrial membrane permeability.	2.56
GOTERM_BP_FAT	Cell morphogenesis involved in neuron differentiation, neuron development.	2.53
GOTERM_BP_FAT	Blood vessel development.	2.52
GOTERM_BP_FAT	Positive regulation of immune system process, B cell differentiation, regulation of steroid metabolic process.	2.51

E.Score - Enrichment Score

Table S4 – List of candidate drugs for lifespan extension. Drugs colored green are experimentally validated

Drug	Main target function	Proposed/Used for	P-Value	Interactions with lifespan-extending genes	Total No: of Genes
Dacinostat	Histone Deacetylase inhibitor(Ganai, 2015)	Cancer	3.72826E-17	10	10
Givinostat	Histone Deacetylase inhibitor(Rambaldi et al., 2010)	Cancer	3.72826E-17	10	10
PCI-24781 (Abexinostat)	Histone Deacetylase inhibitor(Salvador et al., 2013)	Cancer	3.72826E-17	10	10
Belinostat	Histone Deacetylase inhibitor(Steele et al., 2008)	Cancer	4.00865E-16	10	11
Vorinostat	Histone Deacetylase inhibitor(Marks & Breslow, 2007)	Cancer	4.00865E-16	10	11
Pivanex	Histone Deacetylase inhibitor(Reid et al., 2004)	Cancer	7.29936E-14	8	8
Sodium phenylbutyrate	Histone Deacetylase inhibitor(Gilbert et al., 2001)	Cancer	7.29936E-14	8	8
Panobinostat	Histone Deacetylase inhibitor(Ellis et al., 2008)	Cancer	1.35939E-12	10	18
Valproic acid	Histone Deacetylase inhibitor & GABA activator(Phiel et al., 2001)	Cancer & Epilepsy	1.21378E-10	9	19
FK-228*	Histone Deacetylase inhibitor(Piekarz et al., 2009)	Cancer	6.24073E-09	5	5
CHR-3996	Histone Deacetylase inhibitor(Banerji et al., 2012)	Cancer	2.73968E-07	4	4
Choline	Neurotransmitter precursor	Vitamin	6.94313E-07	2	7
Entinostat	Histone Deacetylase inhibitor(Pili et al., 2012)	Cancer	1.33864E-06	4	5
GDC-0068	Serine/Threonine Kinase (Akt) inhibitor(Lin et al., 2013)	Cancer	1.20062E-05	3	3
MK-2206	Serine/Threonine Kinase (Akt) inhibitor(Sangai et al., 2012)	Cancer	1.20062E-05	3	3
Everolimus	mTOR inhibitor(Culp & Wood, 2009)	Cancer	1.74891E-05	4	8
Minaprine	Monoamine Oxidase inhibitor(Gijsman, Geddes, Rendell, Nolen, & Goodwin, 2004)	Depression	3.07631E-05	4	9
Tegaserod	5-Hydroxytryptamine receptor 4 (5-HT4) agonist, Serotonin antagonist(Müller-Lissner et al., 2001)	Irritable bowel syndrome	4.69291E-05	3	4
Romidepsin*	Histone Deacetylase inhibitor(Piekarz et al., 2009)	Cancer	7.69404E-05	4	11
Clodronate	ADP/ATP translocase inhibitor(Diel et al., 1998)	Osteoporosis & Cancer	0.000114645	3	5

*DGIdb erroneously considers FK-228 and Romidepsin as two distinct compounds. In green are drugs previously shown to extend lifespan: Sodium phenylbutyrate (Kang, Benzer, & Min, 2002), valproic acid (Evason, Collins, Huang, Hughes, & Kornfeld, 2008) and everolimus (Spindler, Li, Dhahbi, Yamakawa, & Sauer, 2012).

Table S5 - Categorization of DGIdb's drug-gene interactions into Anti/Pro/Neither classes

Anti	Pro	Neither (Not considered)
inhibitor	potentiator	n/a
antagonist	agonist	binder
blocker	inducer	antibody
inverse agonist	cofactor	other/unknown
antisense	product of	allosteric modulator
negative modulator	stimulator	multitarget
antisense oligonucleotide	activator	modulator
suppressor	partial agonist,agonist	agonist,antagonist
partial antagonist	chaperone	ligand
antagonist, inhibitory allosteric modulator	partial agonist	antagonist, partial agonist
inhibitor, antagonist	modulator,agonist	vaccine
antagonist, multitarget	positive allosteric modulator	adduct
cleavage	agonist, partial agonist	immunotherapy
multitarget, antagonist		antagonist, agonist
inhibitory allosteric modulator		partial agonist, antagonist
inhibitor, competitive		

Tables S6-S17 (in Excel files)

Table S6- Overlap analysis per class - Genome
Table S7- Overlap analysis per disease - Genome
Table S8- Overlap analysis per class - Genome with Publication Bias Correction
Table S9- Overlap analysis per disease - Genome with Publication Bias Correction
Table S10- Overlap analysis per class - Interactome
Table S11- Overlap analysis per disease - Interactome
Table S12- Overlap analysis per class - Interactome with Publication Bias Correction
Table S13- Overlap analysis per disease - Interactome with Publication Bias Correction
Table S14- Overlap analysis per class - including first order partners
Table S15- Overlap analysis per disease - including first order partners
Table S16- Overlap analysis per class - including co-expressed genes
Table S17- Overlap analysis per disease - including co-expressed genes

The tables present the aging gene sets in the columns and disease classes or diseases in rows. For each overlap between an aging gene set and a disease or a diseases class, there are two values, a p-value and the number of CAD-genes. These tables also present a colour code which corresponds to a green background behind the p-value if it is lower than 0.05 - meaning that is a significant value - and with a green background behind CAD-genes if their number is higher than the expected number by chance (not showed); for the both mentioned conditions, if the condition is not verified the background is orange. Only the overlaps with a higher number of CAD-genes than the CAD-genes expected by chance and a p-value lower than 0.05 are considered significant.

Table S18 - Number of genes of aging gene sets

Data Set	Initial Set	PBC 10+ Genome	Interactome	PBC 10+ Interactome	PBC 10+ With partners	PBC 10+ With RNAseq co-expressed genes
Human aging	298	253	294	251	7442	5109
All orthologues						
anti-longevity	448	216	408	214	3792	3942
pro-longevity	421	238	394	237	5628	4557
M. musculus						
anti-longevity	23	17	22	17	730	31
pro-longevity	59	49	57	48	2483	215
D. melanogaster						
anti-longevity	48	25	42	25	1131	77
pro-longevity	87	57	85	57	2855	577
C. elegans						
anti-longevity	381	185	344	183	2994	3545
pro-longevity	290	144	267	144	3286	2649
S. Cerevisiae						
anti-longevity	41	21	38	21	982	28
pro-longevity	13	12	13	12	298	194

Table S19 - Number of diseases at different thresholds for minimum number of genes

Threshold	Num. of diseases
10	130
20	65
30	44
40	25
50	21

Table S20 - Diseases list with the disease class and the number of genes. All shown diseases were analysed per class and diseases marked with asterisk (*) were also analysed individually.

Disease MSH Term	MeSH Disease Class	Num. of Genes
*Hypertension	Cardiovascular	172
*Myocardial Infarction	Cardiovascular	132
*Coronary Disease	Cardiovascular	104
Coronary Artery Disease	Cardiovascular	90
Hypertrophy, Left Ventricular	Cardiovascular	20
Thrombosis	Cardiovascular	22
*Arteriosclerosis	Cardiovascular	45
Diabetic Angiopathies	Cardiovascular	38
*Atherosclerosis	Cardiovascular	31
Graves Disease	Eye	32
Macular Degeneration	Eye	21
Diabetic Retinopathy	Eye	26
*Autoimmune Diseases	Immune System	20
*Hypersensitivity, Immediate	Immune System	32
*Arthritis, Rheumatoid	Musculoskeletal	80
*Osteoporosis	Musculoskeletal	30
*Lung Neoplasms	Neoplasms	92
*Stomach Neoplasms	Neoplasms	66
*Breast Neoplasms	Neoplasms	121
*Prostatic Neoplasms	Neoplasms	90
*Adenocarcinoma	Neoplasms	66
Skin Neoplasms	Neoplasms	28
*Coloretal Neoplasms	Neoplasms	96
Melanoma	Neoplasms	23
Esophageal Neoplasms	Neoplasms	38
Head and Neck Neoplasms	Neoplasms	39
Ovarian Neoplasms	Neoplasms	30
Urinary Blandder Neoplasms	Neoplasms	38
Liver Neoplasms	Neoplasms	30
Mouth Neoplasms	Neoplasms	31
Uterine Cervical Neoplasms	Neoplasms	21
Endometrial Neoplasms	Neoplasms	24
*Alzheimer Disease	Nervous System	115
*Parkinson Disease	Nervous System	50
*Multiple Sclerosis	Nervous System	49
*Diabetes Mellitus, Type 1	Nutritional and Metabolic	100
*Diabetes Mellitus, Type 2	Nutritional and Metabolic	219
*Obesity	Nutritional and Metabolic	127
*Asthma	Respiratory Tract	122
Pulmonary Disease, Chronic Obstruction	Respiratory Tract	33

Supplementary Figures

Figure S1: Similar top functional annotation clusters from the LongevityMap in two backgrounds. (Higher ranked clusters obtained from default background also have higher rank when using LongevityMap genes as background)

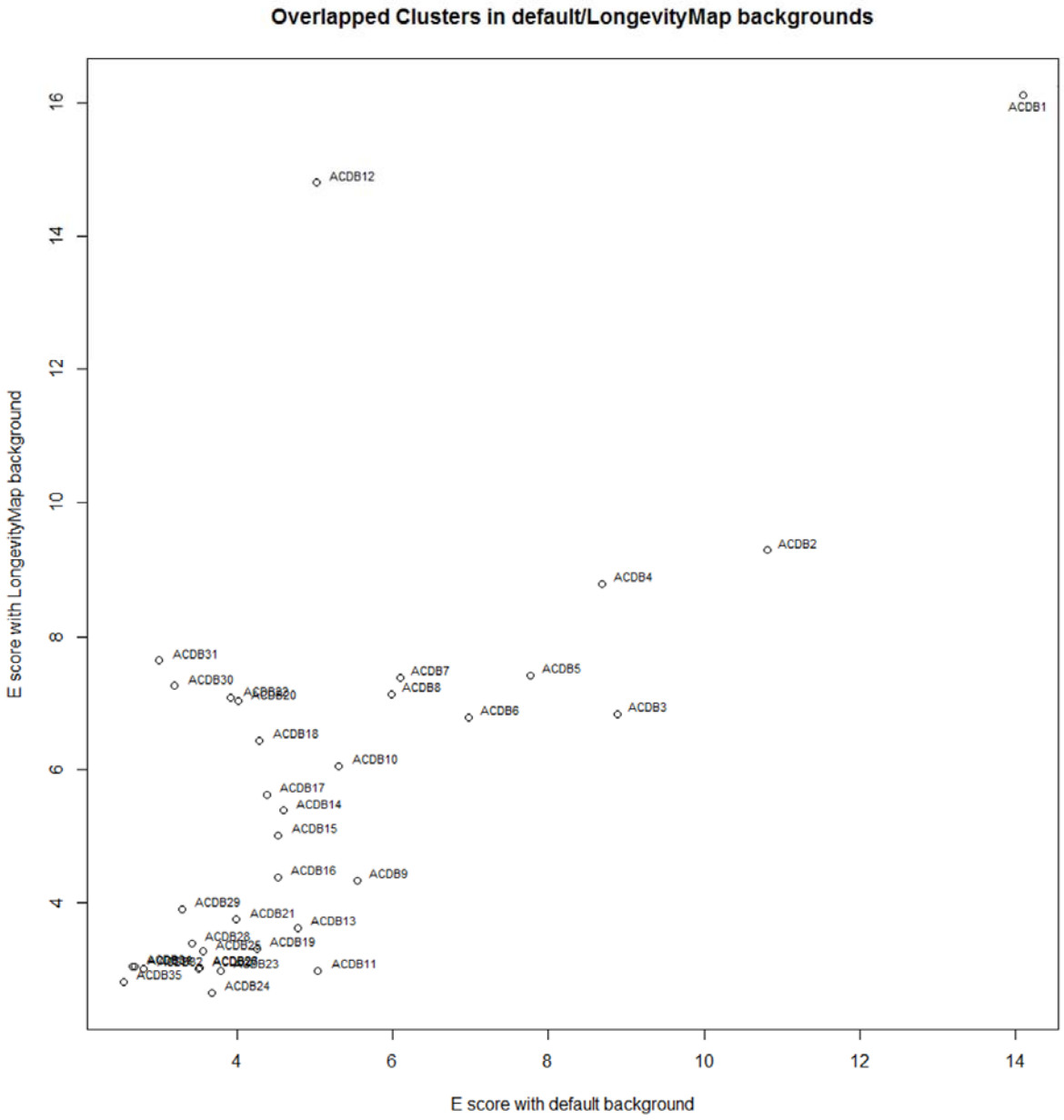


Figure S2: Analysis of publications number per gene for the human genome. This graph shows the variation of the number of genes for different thresholds of publications per gene. Thresholds between 8 and 20 were assessed.

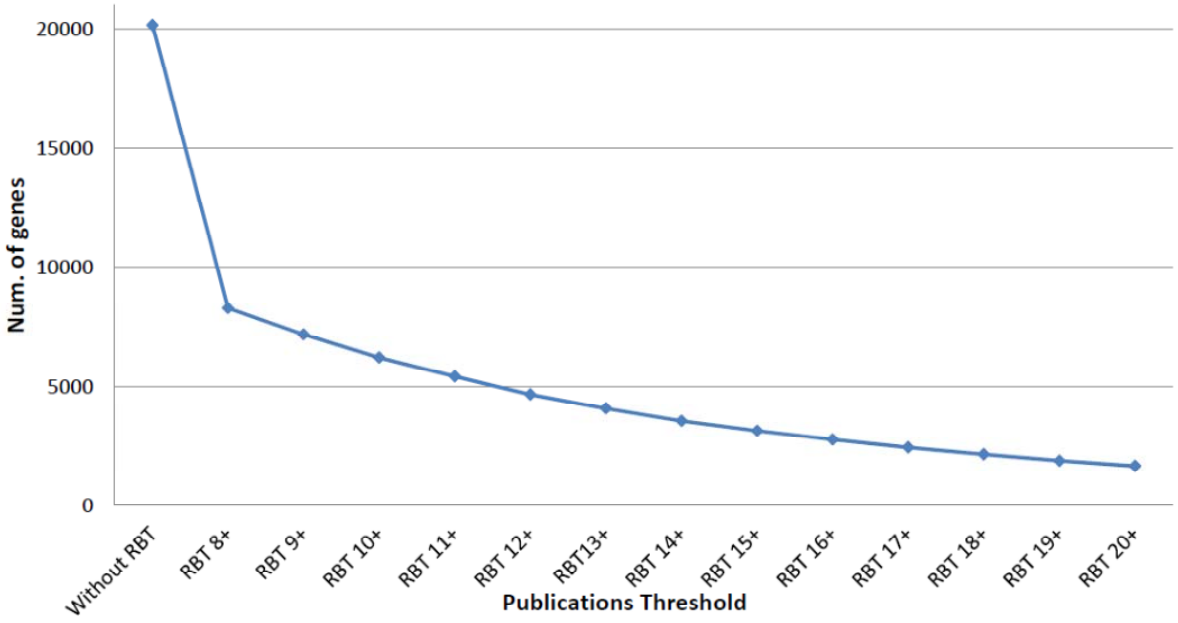
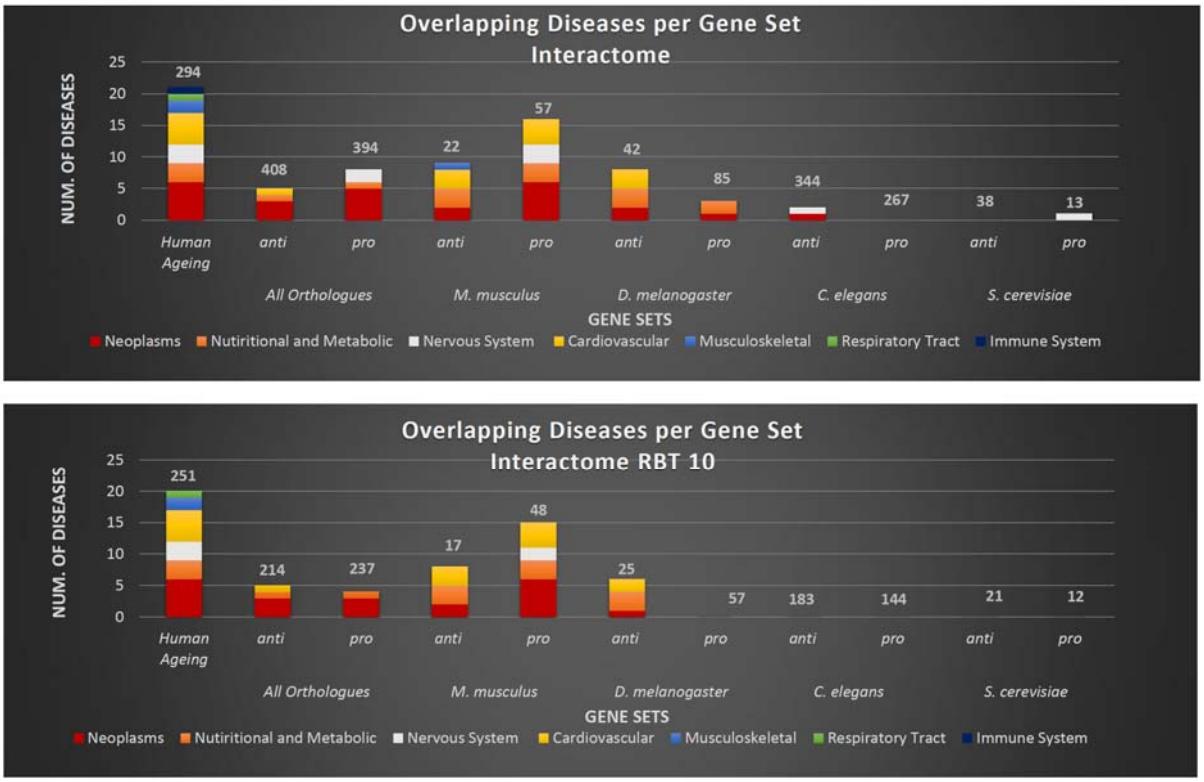


Figure S3: Number of significant diseases per gene set - Interactome without and with PBC. The graph on top summarizes the number of significant overlapping diseases per gene set in analysis without PBC and the graph on the bottom is relative to the analysis with PBC, both using the interactome as background without and with PBC, respectively. Different colours in each column correspond to each class of diseases. Above each column is the number of genes in the aging gene set.



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