

Neurodegenerative diseases from systems medicine perspective

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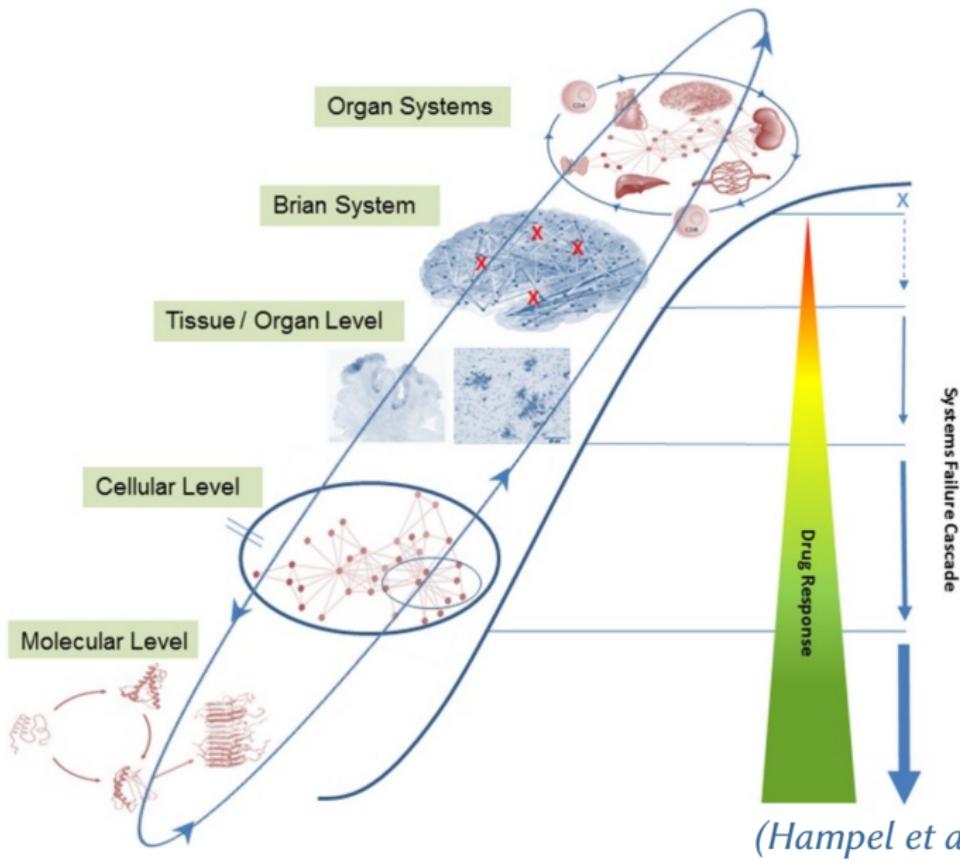
Institut Hospital del Mar
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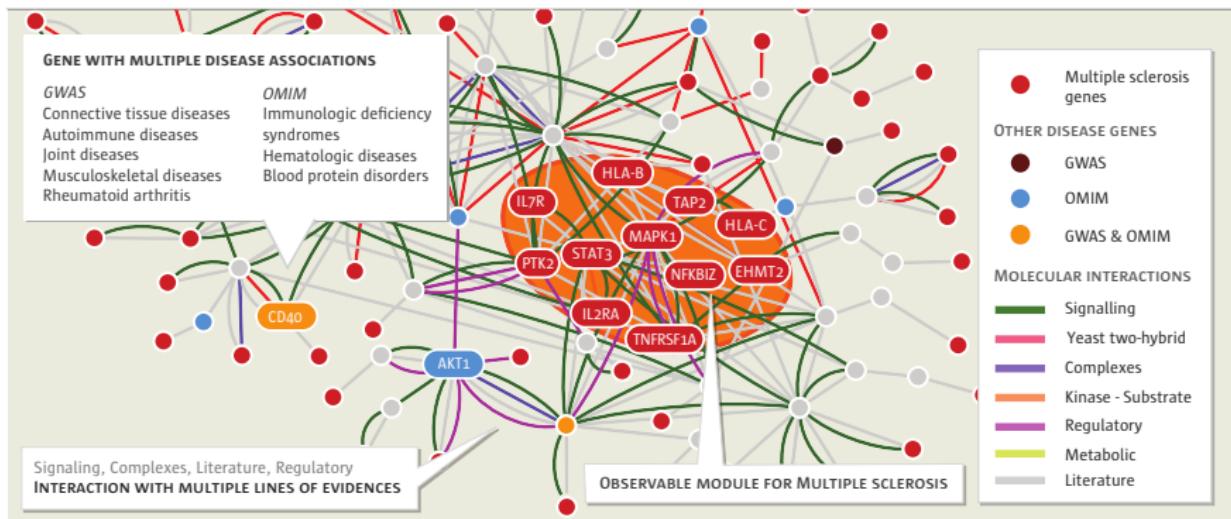
RESEARCH
PROGRAMME
ON BIOMEDICAL
INFORMATICS



Systems medicine



Systems-level representation of the cellular network

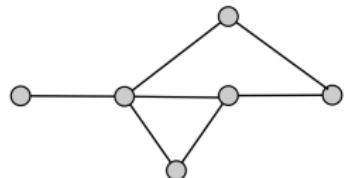


(Menche et al., 2015, Science)

Recent advances in *omics have given rise to rich data sets:
Genome / Transcriptome / Proteome / Epigenome / Exosome /
Metabolome / Microbiome / ...

Network representation

Networks (in biology) are formally defined as **Graphs** (in math & computer science)



$G(V, E)$

V: Vertices (nodes)

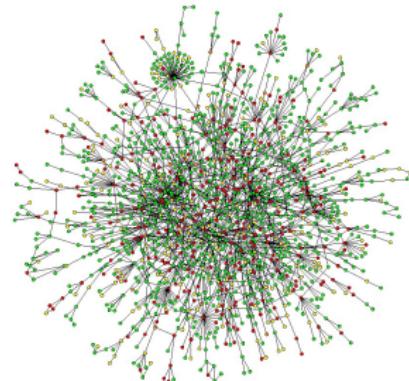
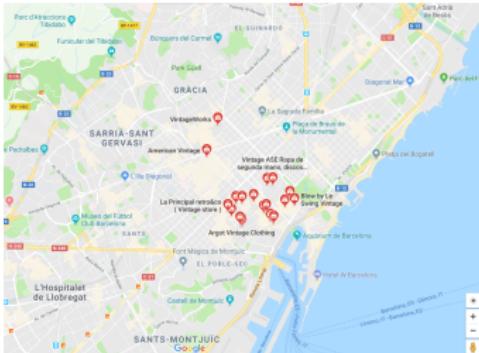
E: Edges (interactions) connecting vertices

In a biological network, vertices can be of different types:

- proteins
- genes
- metabolites
- ...

And edges correspond to various types of interactions between them 4

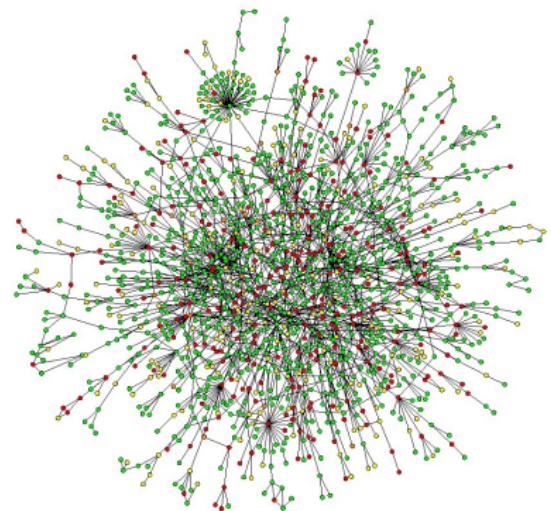
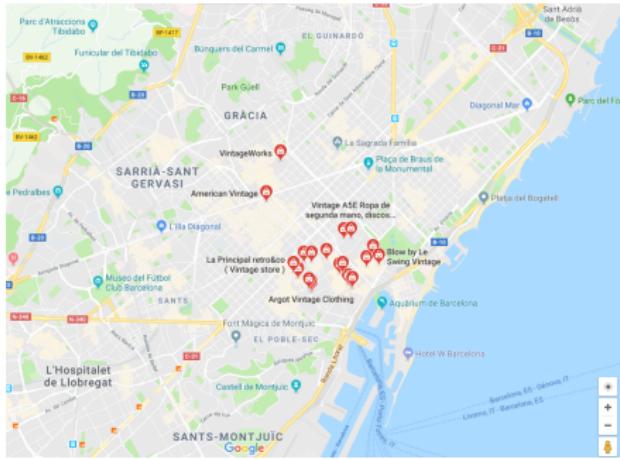
Interactome: The cellular map



(Barabási and Oltvai, 2004, Nat Rev Genet)

- Proteins “talk to each other” by physically interacting with each other
 - These interactions are essential for performing biological processes
 - The network of interactions between proteins: **Interactome**

How to generate such a map for the cell?



Interactome generation: Protein interaction data

Protein-protein interaction (PPI) data is spread across various repositories

KEGG

DIP

Reactome

MIPS



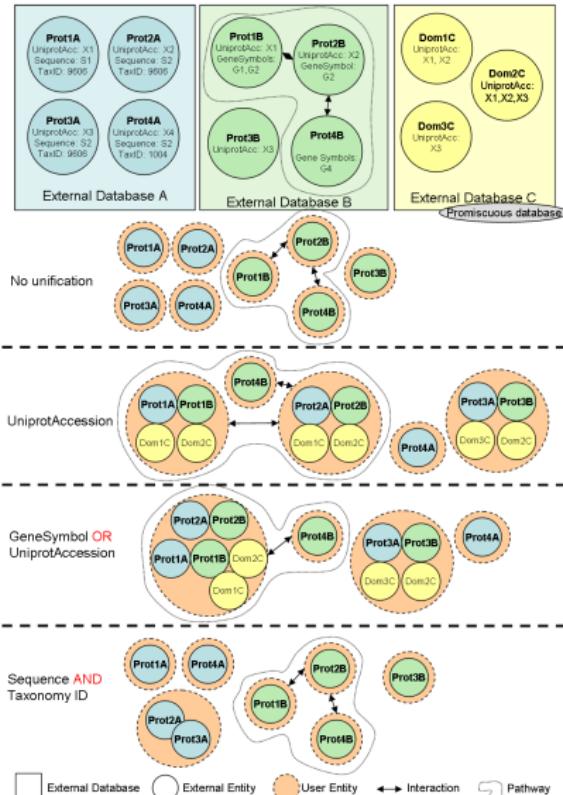
IntAct

STRING

MINT

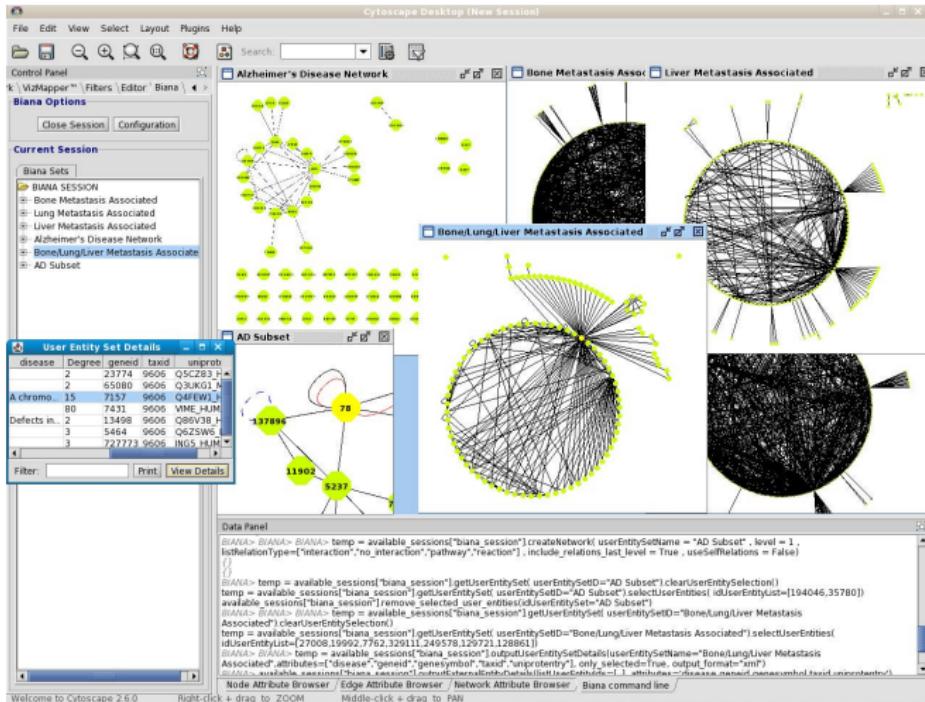
BioGrid

Interactome generation: Integrating protein interaction data



(Garcia-Garcia et al., 2010, BMC Bioinformatics)

Interactome visualization and analysis



Cytoscape: A tool to visualize and analyze biological networks
(Cline et al., 2007, Nat Protoc)

Network analysis for understanding a system

Facebook friends

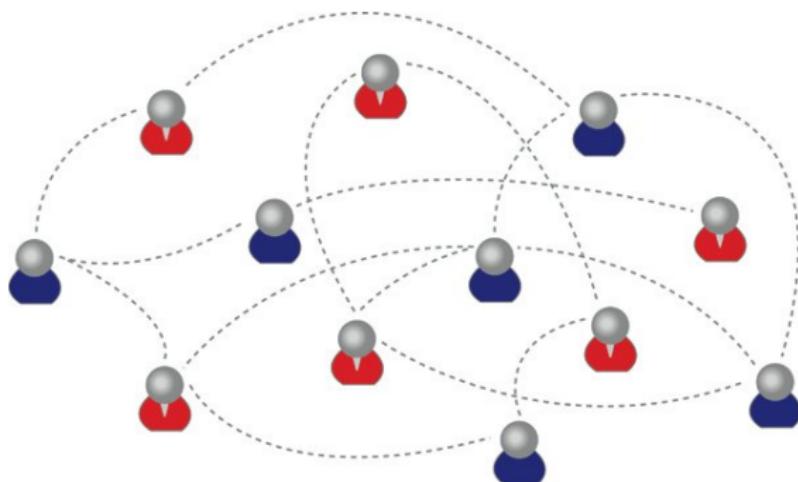
~85%

Network analysis for understanding a system

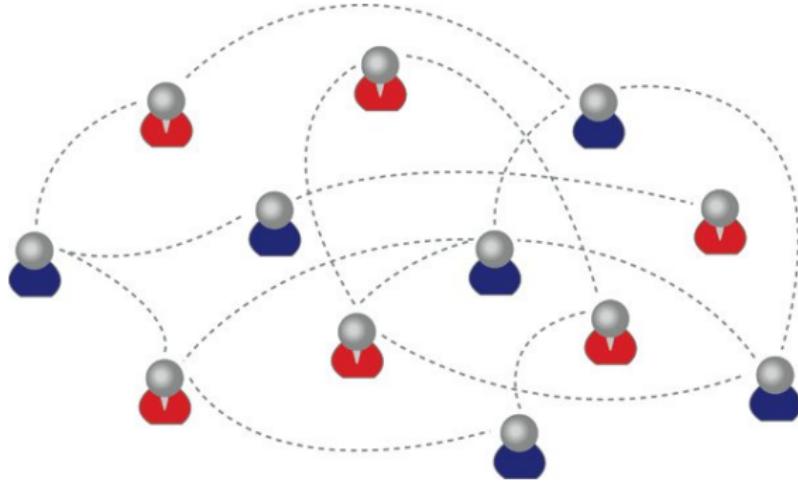
Percentage of your Facebook friends from the same country

(Ugander et al., 2011, arXiv:1111.4503)

~85%

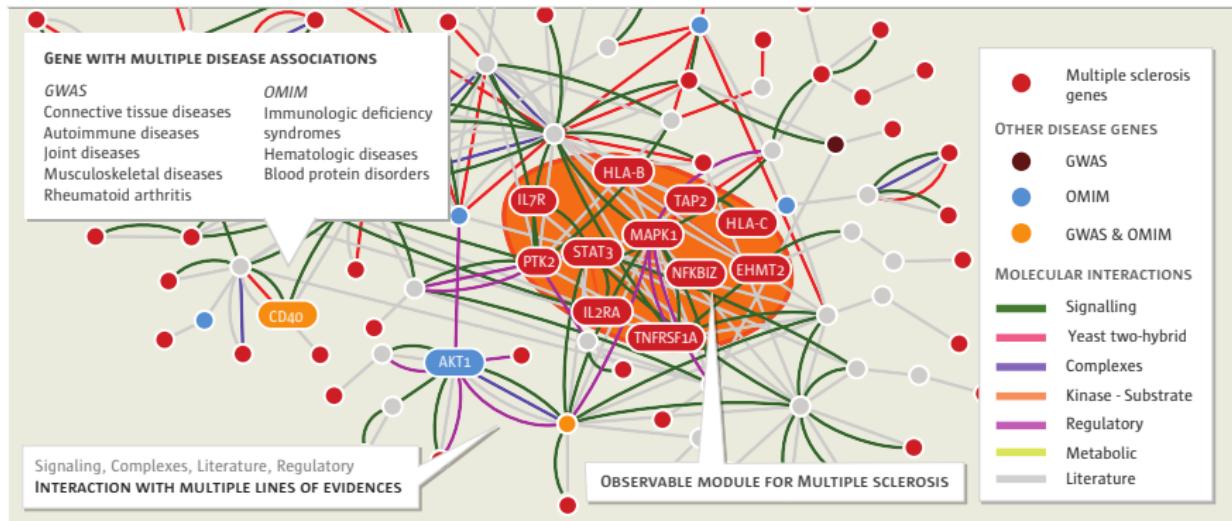


How can one use interactome to extract biologically meaningful information?



Similarly, proteins that perform similar functions interact with each other (guilt-by-association principle)

Interactome analysis: Guilt-by-association

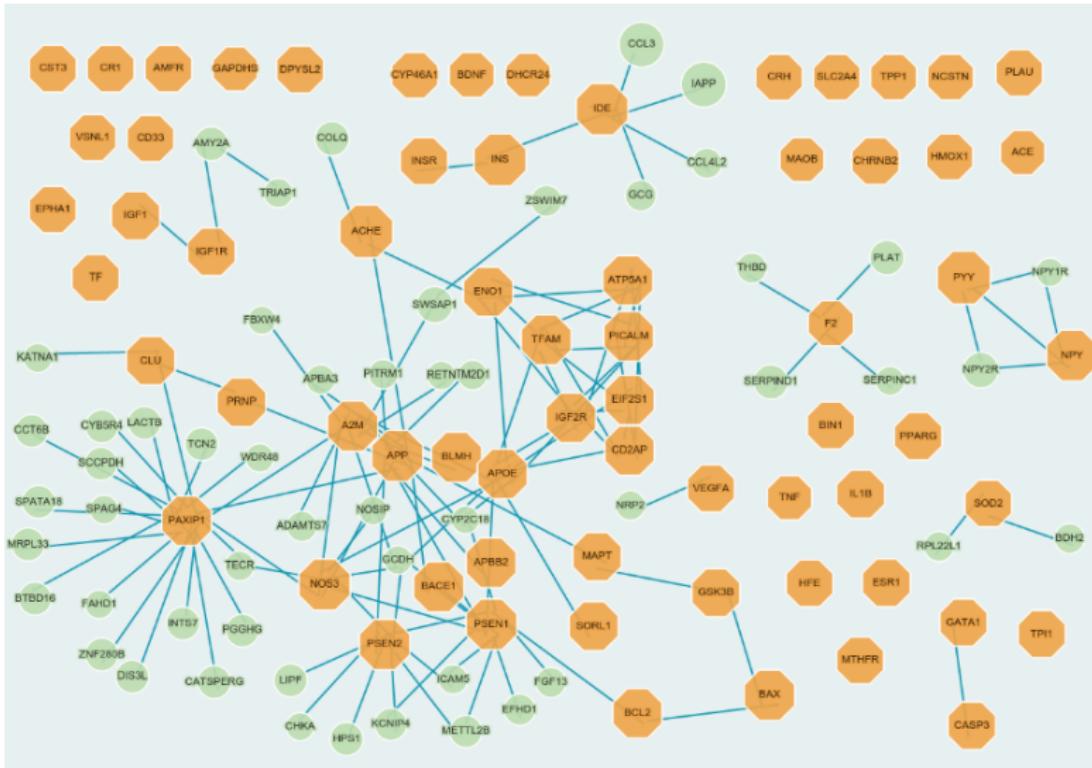


(Menche et al., 2015, Science)

Proteins that perform similar functions or involved in similar diseases interact with each other (guilt-by-association)

Neurodegenerative diseases: A systems-level perspective

Alzheimer's Disease (AD)



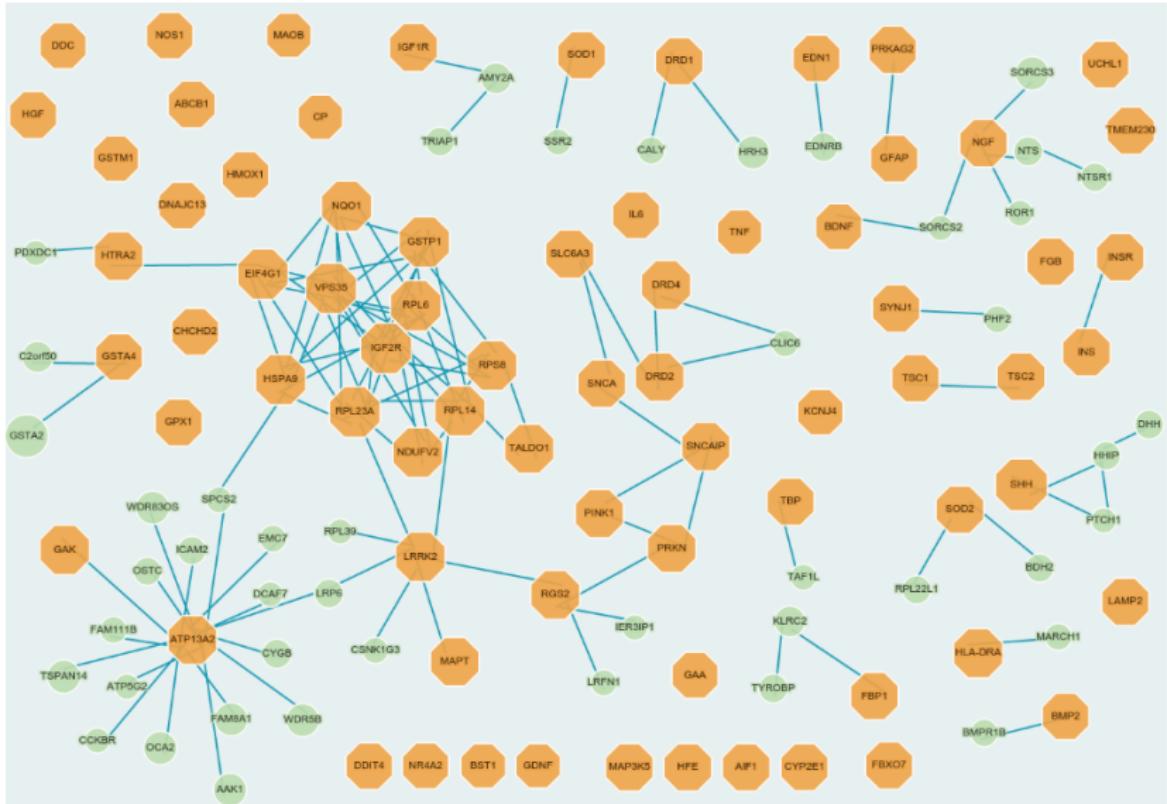
Proteins of genes known to be involved in AD (orange hexagons,
sources: OMIM, DisGeNET, GUILDFy2)

Alzheimer's Disease (AD)

GO ID	GO term name	Number of genes	Total number of genes	Adj. P-value
GO:1990535	neuron projection maintenance	5	6	1.83e-11
GO:1901216	positive regulation of neuron death	6	19	3.75e-10
GO:1904646	cellular response to amyloid-beta	6	22	1.02e-09
GO:1902430	negative regulation of amyloid-beta formation	4	7	2.19e-08
GO:0090647	modulation of age-related behavioral decline	4	7	2.19e-08
GO:0030335	positive regulation of cell migration	9	151	3.03e-08
GO:0014910	regulation of smooth muscle cell migration	3	4	5.15e-07
GO:2001240	negative regulation of extrinsic apoptotic signaling pathway in absence of ligand	4	16	8.29e-07
GO:0043243	positive regulation of protein complex disassembly	3	5	1.28e-06
GO:0006509	membrane protein ectodomain proteolysis	4	18	1.84e-06
GO:0010628	positive regulation of gene expression	9	253	2.55e-06
GO:0035094	response to nicotine	3	6	2.56e-06
GO:0007611	learning or memory	4	21	2.89e-06
GO:0032092	positive regulation of protein binding	5	46	3.57e-06
GO:0045840	positive regulation of mitotic nuclear division	4	22	4.33e-06
GO:0045429	positive regulation of nitric oxide biosynthetic process	4	22	4.33e-06
GO:0050435	amyloid-beta metabolic process	3	7	4.46e-06
GO:0042982	amyloid precursor protein metabolic process	3	8	7.11e-06
GO:0045821	positive regulation of glycolytic process	3	8	7.11e-06
GO:0043066	negative regulation of apoptotic process	9	271	8.06e-06

Most relevant functions among AD-related genes

Parkinson Disease (PD)



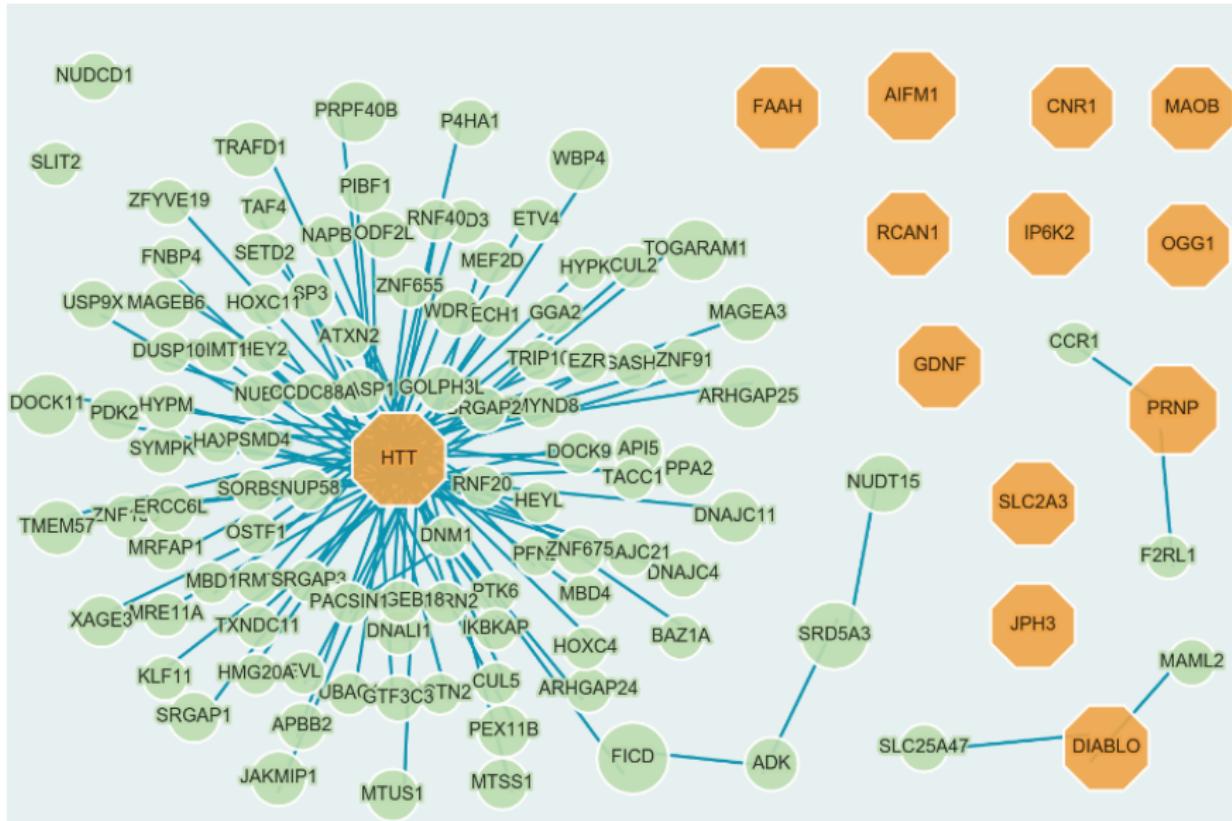
Proteins of genes known to be involved in PD

Parkinson Disease (PD)

GO ID	GO term name	Number of genes	Total number of genes	Adj. P-value
GO:1901215	negative regulation of neuron death	5	20	7.41e-08
GO:0000187	activation of MAPK activity	6	39	7.6e-08
GO:0006749	glutathione metabolic process	5	21	9.68e-08
GO:0099074	mitochondrion to lysosome transport	3	3	1.75e-07
GO:1905606	regulation of presynapse assembly	3	3	1.75e-07
GO:0048661	positive regulation of smooth muscle cell proliferation	5	25	2.48e-07
GO:0010821	regulation of mitochondrion organization	4	11	3.05e-07
GO:0030335	positive regulation of cell migration	8	151	1.01e-06
GO:0043243	positive regulation of protein complex disassembly	3	5	1.74e-06
GO:1901216	positive regulation of neuron death	4	19	3.46e-06
GO:0010628	positive regulation of gene expression	9	253	5.93e-06
GO:0016242	negative regulation of macroautophagy	3	8	9.6e-06
GO:0008344	adult locomotory behavior	3	8	9.6e-06
GO:0043524	negative regulation of neuron apoptotic process	5	54	1.19e-05
GO:0050709	negative regulation of protein secretion	3	14	2.04e-05
GO:0000165	MAPK cascade	4	31	2.67e-05
GO:0033138	positive regulation of peptidyl-serine phosphorylation	5	63	2.78e-05
GO:0000422	autophagy of mitochondrion	3	11	2.79e-05
GO:0032930	positive regulation of superoxide anion generation	3	11	2.79e-05
GO:0040012	regulation of locomotion	2	2	3.17e-05

Most relevant functions among PD-related genes

Huntington Disease (HD)



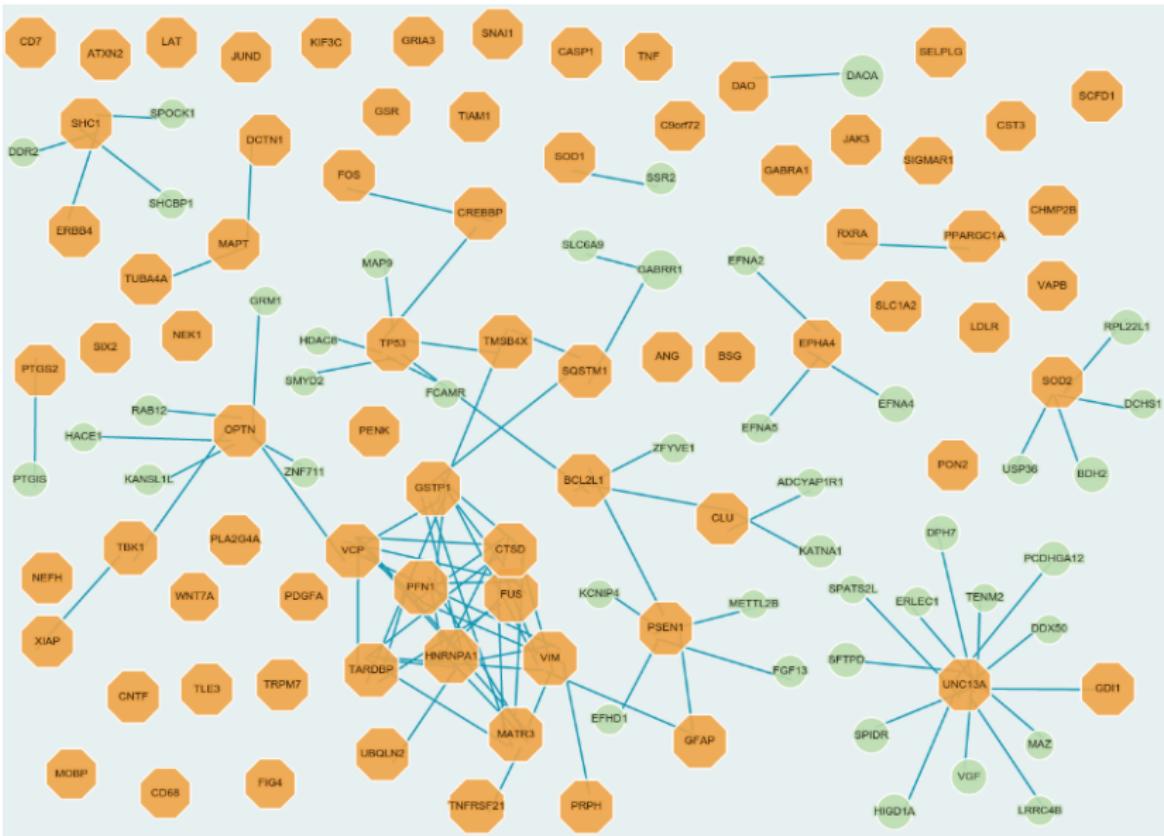
Proteins of genes known to be involved in HD

Huntington Disease (HD)

GO ID	GO term name	Number of genes	Total number of genes	Adj. P-value
GO:0031648	protein destabilization	2	30	0.000392
GO:0006979	response to oxidative stress	2	44	0.000846
GO:0021784	postganglionic parasympathetic fiber development	1	1	0.000996
GO:0038171	cannabinoid signaling pathway	1	1	0.000996
GO:1905337	positive regulation of aggrphagy	1	1	0.000996
GO:1901291	negative regulation of double-strand break repair via single-strand annealing	1	1	0.000996
GO:0017064	fatty acid amide hydrolase activity	1	1	0.000996
GO:1902992	negative regulation of amyloid precursor protein catabolic process	1	2	0.00199
GO:0009062	fatty acid catabolic process	1	2	0.00199
GO:0032770	positive regulation of monooxygenase activity	1	2	0.00199
GO:1905664	regulation of calcium ion import across plasma membrane	1	2	0.00199
GO:0060688	regulation of morphogenesis of a branching structure	1	2	0.00199
GO:0051584	regulation of dopamine uptake involved in synaptic transmission	1	2	0.00199
GO:1902938	regulation of intracellular calcium activated chloride channel activity	1	2	0.00199
GO:0004949	cannabinoid receptor activity	1	2	0.00199
GO:1903599	positive regulation of autophagy of mitochondrion	1	3	0.00299
GO:0031587	positive regulation of inositol 1,4,5-trisphosphate-sensitive calcium-release channel activity	1	3	0.00299
GO:1904659	glucose transmembrane transport	1	3	0.00299
GO:0033158	regulation of protein import into nucleus, translocation	1	3	0.00299
GO:1902951	negative regulation of dendritic spine maintenance	1	3	0.00299

Most relevant functions among HD-related genes

Amyotrophic Lateral Sclerosis (ALS)



Proteins of genes known to be involved in ALS

Amyotrophic Lateral Sclerosis (ALS)

GO ID	GO term name	Number of genes	Total number of genes	Adj. P-value
GO:2001171	positive regulation of ATP biosynthetic process	3	5	1.96e-06
GO:0032930	positive regulation of superoxide anion generation	3	11	3.15e-05
GO:0097252	oligodendrocyte apoptotic process	2	2	3.43e-05
GO:0000303	response to superoxide	2	2	3.43e-05
GO:0004784	superoxide dismutase activity	2	2	3.43e-05
GO:1902230	negative regulation of intrinsic apoptotic signaling pathway in response to DNA damage	3	13	5.41e-05
GO:0006914	autophagy	4	36	5.71e-05
GO:1905907	negative regulation of amyloid fibril formation	2	3	0.000103
GO:1901216	positive regulation of neuron death	3	19	0.000179
GO:0031622	positive regulation of fever generation	2	4	0.000205
GO:0019048	modulation by virus of host morphology or physiology	2	4	0.000205
GO:0045893	positive regulation of transcription, DNA-templated	10	430	0.000207
GO:0043524	negative regulation of neuron apoptotic process	4	54	0.000263
GO:0008217	regulation of blood pressure	3	22	0.00028
GO:0045429	positive regulation of nitric oxide biosynthetic process	3	22	0.00028
GO:0044212	transcription regulatory region DNA binding	6	162	0.000382
GO:0005507	copper ion binding	3	26	0.000465
GO:0019430	removal of superoxide radicals	2	7	0.000708
GO:0042802	identical protein binding	5	127	0.000787
GO:2000785	regulation of autophagosome assembly	2	8	0.00094

Most relevant functions among ALS-related genes

*Shared functional components
across neurodegenerative diseases*

Alzheimer's Disease and Parkinson Disease

GO ID	GO term name	P-value 1	P-value 2	Comb. p-value
GO:1901216	positive regulation of neuron death	1.5E-08	2.4E-05	1.1E-11
GO:1990535	neuron projection maintenance	3.9E-10	1.3E-03	1.4E-11
GO:0030335	positive regulation of cell migration	5.9E-07	4.0E-05	6.0E-10
GO:0043243	positive regulation of protein complex disassembly	7.9E-06	7.7E-06	1.5E-09
GO:0055072	iron ion homeostasis	1.5E-06	8.9E-05	3.1E-09
GO:0000187	activation of MAPK activity	4.6E-04	1.4E-06	1.5E-08
GO:1901215	negative regulation of neuron death	8.1E-04	8.7E-07	1.6E-08
GO:0000165	MAPK cascade	9.2E-06	1.8E-04	3.5E-08
GO:0048661	positive regulation of smooth muscle cell proliferation	1.6E-03	2.9E-06	9.2E-08
GO:0010628	positive regulation of gene expression	6.1E-05	3.0E-04	3.4E-07

Alzheimer's Disease and Parkinson Disease

AD (1) common PD (2)



N common	N1	N2	N total	Odds Ratio	P value
165	593	653	49064	37.906	5.2E-171

*Perez-Rubio et al., 2017, Sci Rep
Aguirre-Plans et al., submitted*

Alzheimer's Disease and Huntington Disease

GO ID	GO term name	P-value 1	P-value 2	Comb. p-value
GO:0016628	oxidoreductase activity, acting on the CH-CH group of donors, NAD or NADP as acceptor	2.6E-04	2.7E-02	9.0E-05
GO:0008286	insulin receptor signaling pathway	1.4E-03	2.0E-02	3.2E-04
GO:0002020	protease binding	8.5E-04	4.5E-02	4.3E-04
GO:0003151	outflow tract morphogenesis	2.0E-03	2.5E-02	5.4E-04
GO:0008017	microtubule binding	1.2E-02	1.1E-02	1.3E-03
GO:1902992	negative regulation of amyloid precursor protein catabolic process	1.9E-02	1.8E-02	3.0E-03
GO:1905664	regulation of calcium ion import across plasma membrane	1.9E-02	1.8E-02	3.0E-03
GO:1902938	regulation of intracellular calcium activated chloride channel activity	1.9E-02	1.8E-02	3.0E-03
GO:0019966	interleukin-1 binding	1.9E-02	1.8E-02	3.0E-03
GO:1902951	negative regulation of dendritic spine maintenance	2.8E-02	2.7E-02	6.2E-03

Alzheimer's Disease and Huntington Disease

AD (1) common HD (2)



N common	N1	N2	N total	Odds Ratio	P value
14	593	240	49064	5.162	1.7E-06

Alzheimer's Disease and Amyotrophic Lateral Sclerosis

GO ID	GO term name	P-value 1	P-value 2	Comb. p-value
GO:1901216	positive regulation of neuron death	1.5E-08	6.6E-04	2.5E-10
GO:1904646	cellular response to amyloid-beta	3.9E-08	1.7E-02	1.5E-08
GO:0030335	positive regulation of cell migration	5.9E-07	3.7E-02	4.1E-07
GO:0007613	memory	3.1E-05	7.7E-04	4.5E-07
GO:0000165	MAPK cascade	9.2E-06	2.8E-03	4.8E-07
GO:0045429	positive regulation of nitric oxide biosynthetic process	4.7E-05	1.0E-03	8.6E-07
GO:0014910	regulation of smooth muscle cell migration	3.2E-06	3.6E-02	2.0E-06
GO:1902004	positive regulation of amyloid-beta formation	6.4E-05	2.9E-03	3.1E-06
GO:0031622	positive regulation of fever generation	5.1E-04	5.0E-04	4.1E-06
GO:2001171	positive regulation of ATP biosynthetic process	4.6E-02	7.5E-06	5.5E-06

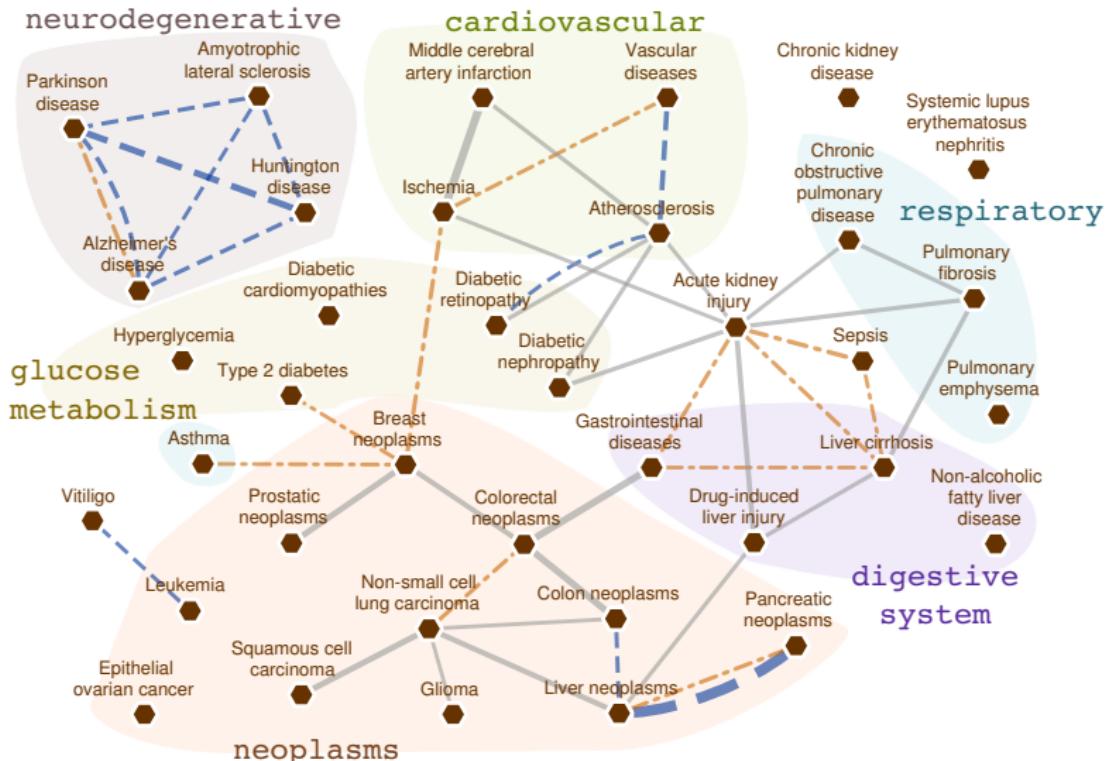
Alzheimer's Disease and Amyotrophic Lateral Sclerosis

AD (1) common ALS (2)



N common	N1	N2	N total	Odds Ratio	P value
125	593	393	49064	48.040	3.2E-142

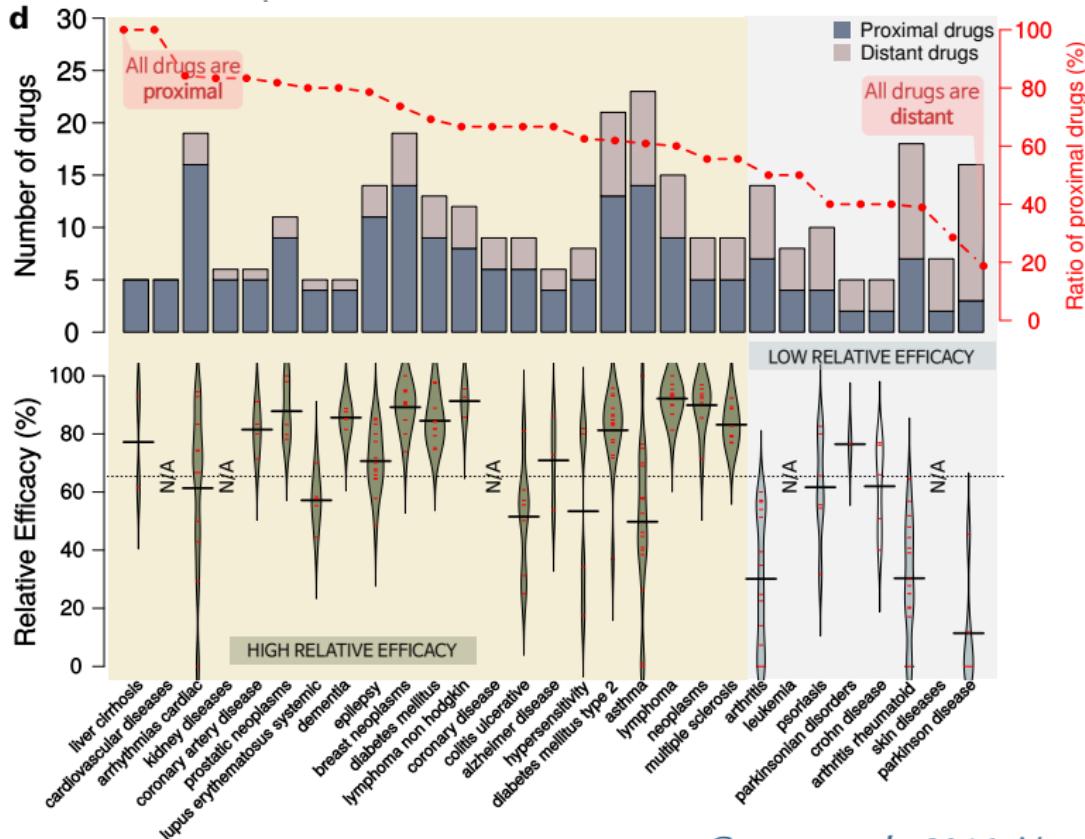
From interactome to diseasesome, the network of diseases



Goh et al., 2007, PNAS
Cuadrado et al., to appear in Pharm Rev

Neurodegenerative diseases: Challenges and opportunities

We still do not completely understand the disease pathology



Genetic heterogeneity among patients

IMPRECISION MEDICINE

For every person they do help (blue), the ten highest-grossing drugs in the United States fail to improve the conditions of between 3 and 24 people (red).

1. ABILIFY (aripiprazole)
Schizophrenia



2. NEXIUM (esomeprazole)
Heartburn



3. HUMIRA (adalimumab)
Arthritis



4. CRESTOR (rosuvastatin)
High cholesterol



5. CYMBALTA (duloxetine)
Depression



6. ADVAIR DISKUS (fluticasone propionate)
Asthma



7. ENBREL (etanercept)
Psoriasis



8. REMICADE (infliximab)
Crohn's disease



9. COPAXONE (glatiramer acetate)
Multiple sclerosis



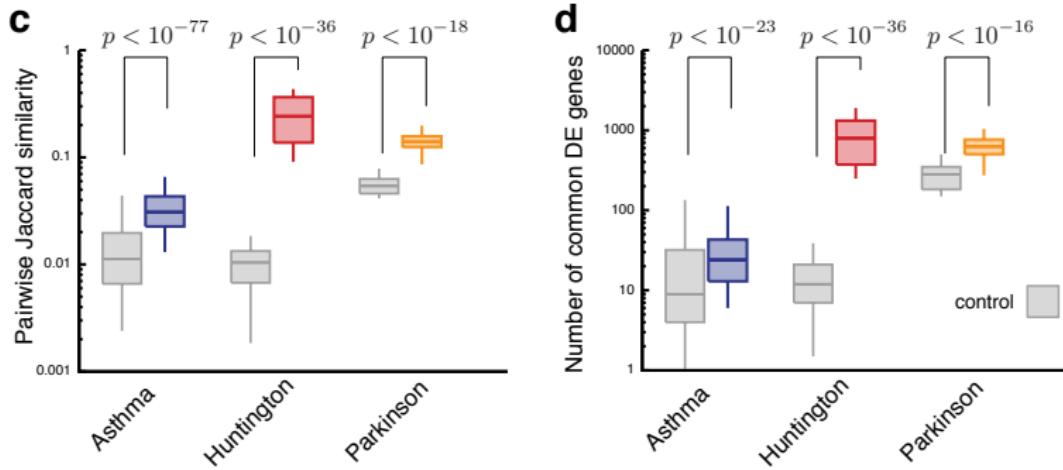
10. NEULASTA (pegfilgrastim)
Neutropenia



Based on published number needed to treat (NNT) figures. For a full list of references, see Supplementary Information at go.nature.com/4dr78f.

Schork, 2015, Nature

Not all disease-associated genes are altered in a given patient



The overlap between perturbed genes of two individuals with the same disease

- is low (< 30%), suggesting high heterogeneity at the transcription level
- is higher than the overlap between the PeePs of healthy subjects

Menche et al., 2017, Npj Sys Bio & App

Several resources for systems medicine and interactome analysis

Resource	URL
<i>Disease-gene information</i>	
DisGeNET	www.disgenet.org
<i>Interactome generation</i>	
BIANA (web server)	sbi.imim.es/BIANA.php
<i>Interactome visualization and analysis</i>	
Cytoscape	www.cytoscape.org
GUILDify web server	sbi.imim.es/GUILDify2.php
<i>Transcriptomic analysis</i>	
PEPPER R package	github.com/emreg00/pepper

Concluding remarks

- Interactome, the network of interactions between proteins, provides a framework for understanding and characterizing biological processes
- Network medicine is an emerging field that aims to use interactome-based analyzes to identify genes associated to diseases and develop novel therapeutics
- The biological mechanisms underlying neurodegenerative diseases are highly complex, often involving perturbations on multiple genes
- These genes are involved in diverse biological functions, some of which are common across different neurodegenerative diseases
- Genetic heterogeneity among patients both poses a challenge and opportunity in developing personalized treatments

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