Network approaches to find mitochondrial disease genes and diabetes comorbidity

소셜네트워크 분석 방법을 응용한 당뇨병 합병증과 미토콘드리아 질병유전자 탐색

POSTECH
생명과학과 김상욱

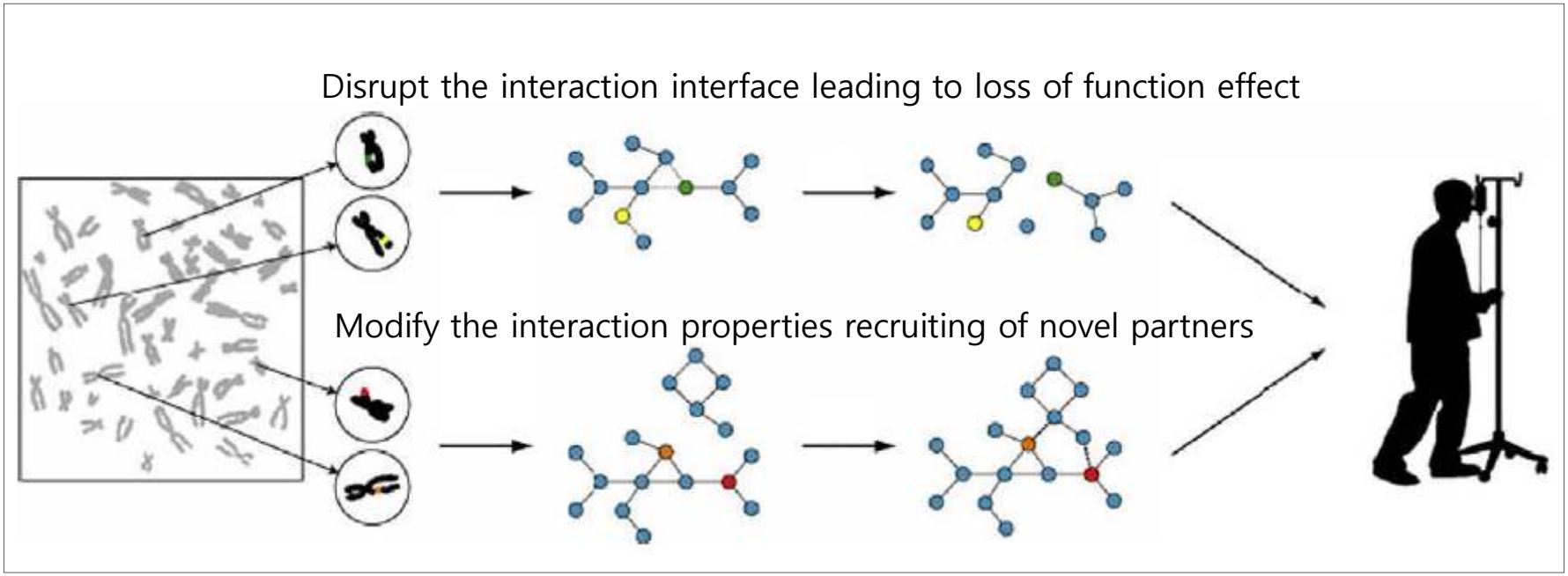
Structural Bioinformatics Laboratory
Pohang University of Science and Technology

Acknowledgement

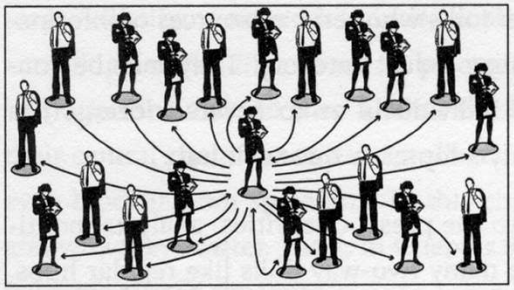
SBI lab

Jou-hyun Jeon
Jae-seong Yang
Solip Park
Yonghwan Choi
Yoonsup Choi
Jinho Kim
HyunJun Nam
JiHye Hwang
Inhae Kim
Youngeun Shin
Sung gyu Han

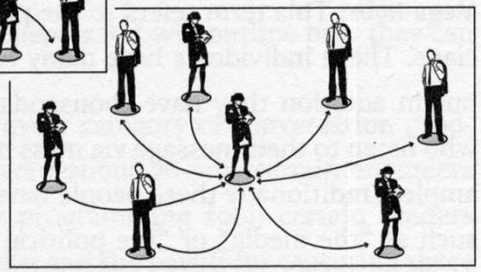
Disease mechanism in the protein interaction network



Society

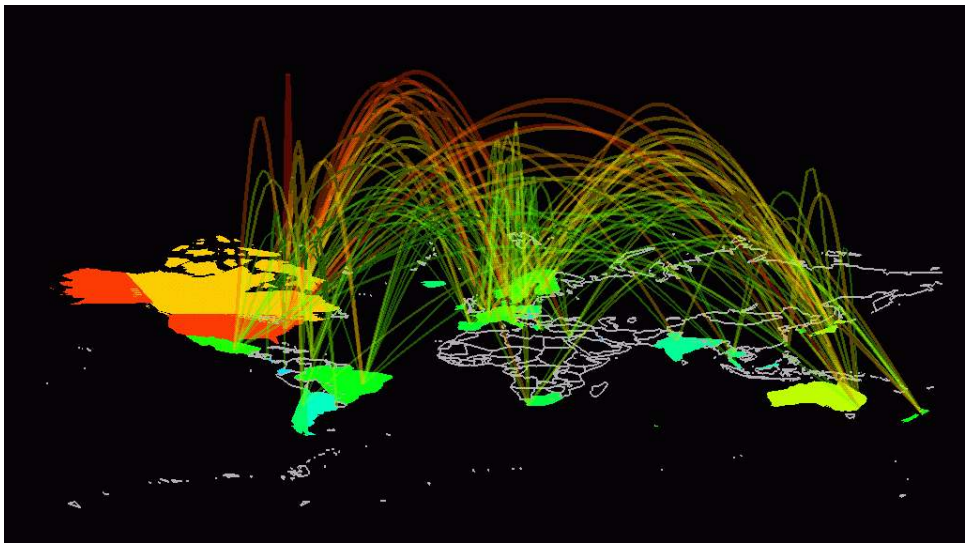


Mega-Hub. An MTV veejay spreads the word to thousands or millions of people through one-way links.

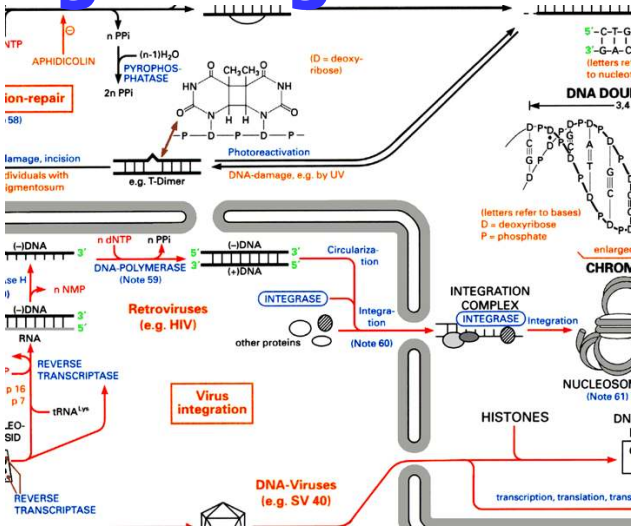


Hub. This undergraduate has spread the word to seven other people through two-way links.

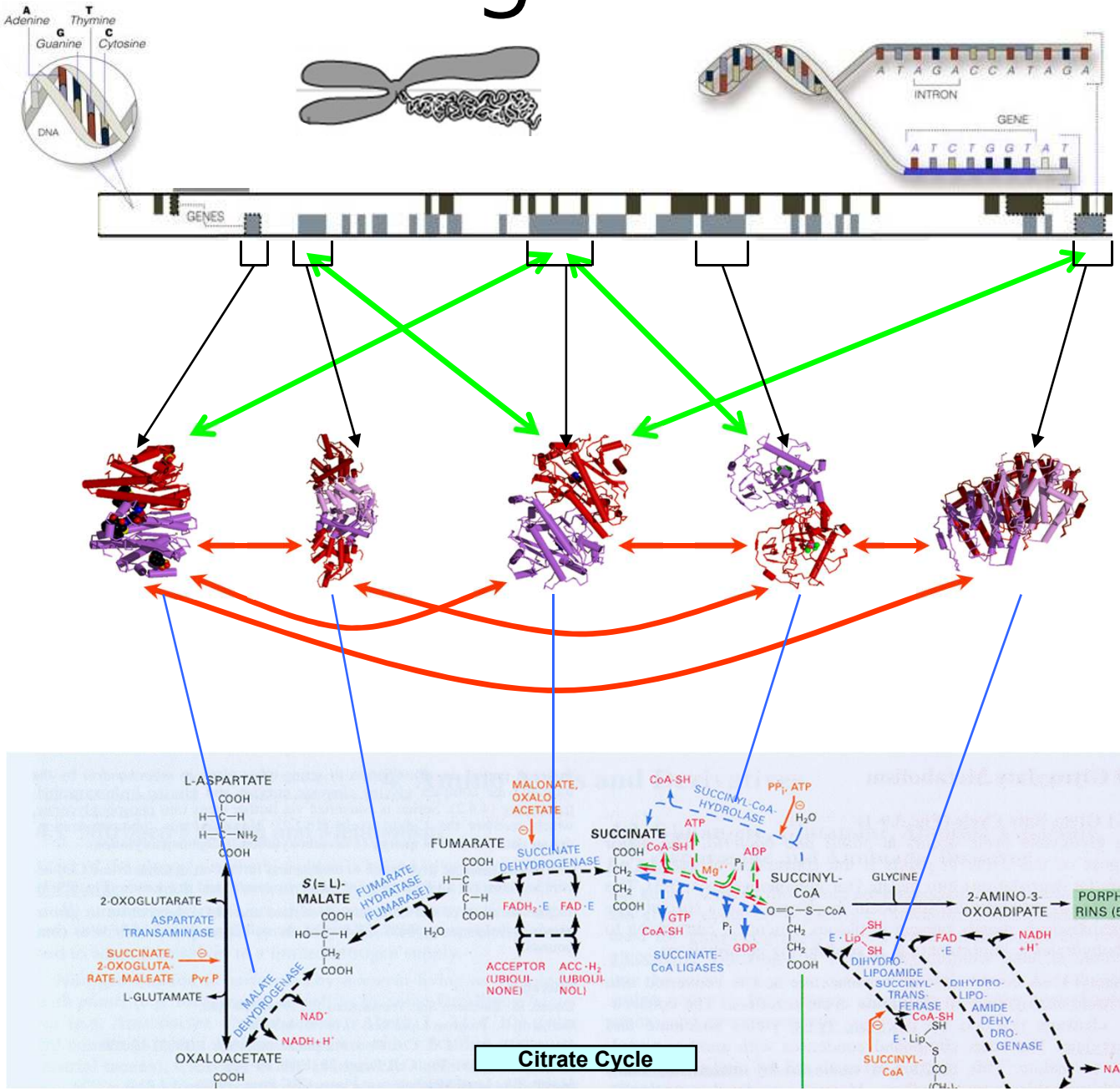
Internet



Biological signaling network



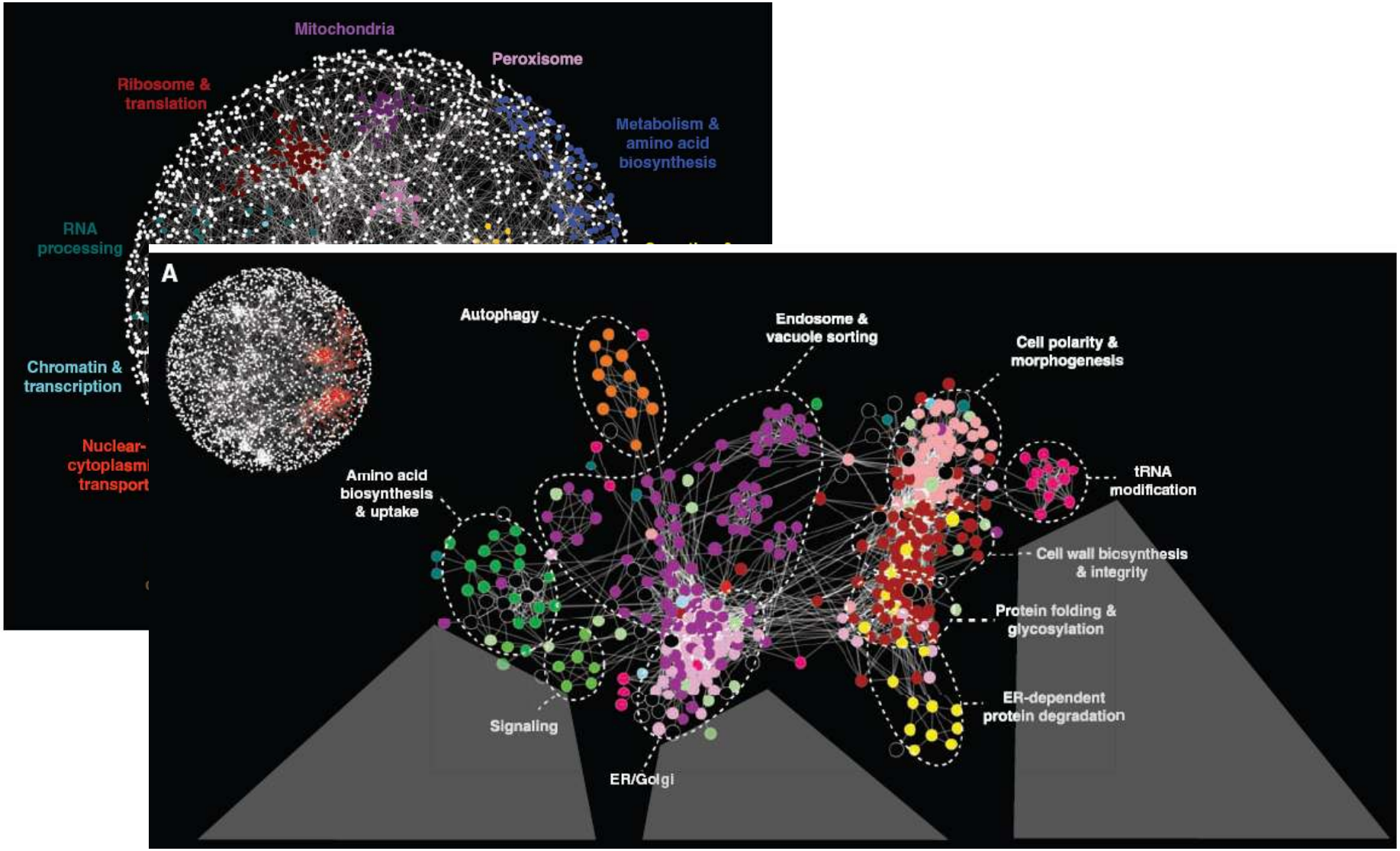
Biological Networks



GENOME

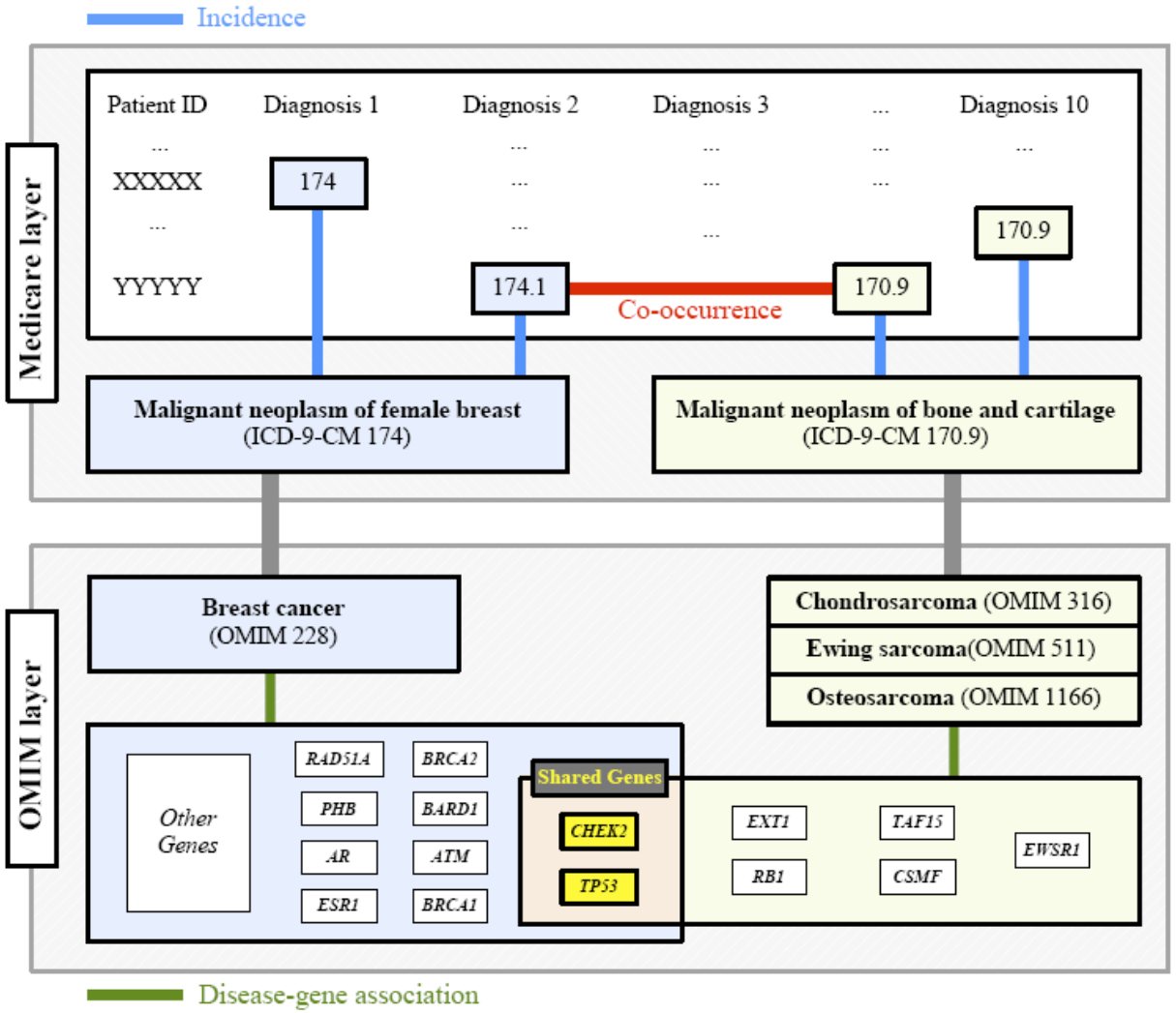
PROTEOME

PHENOME

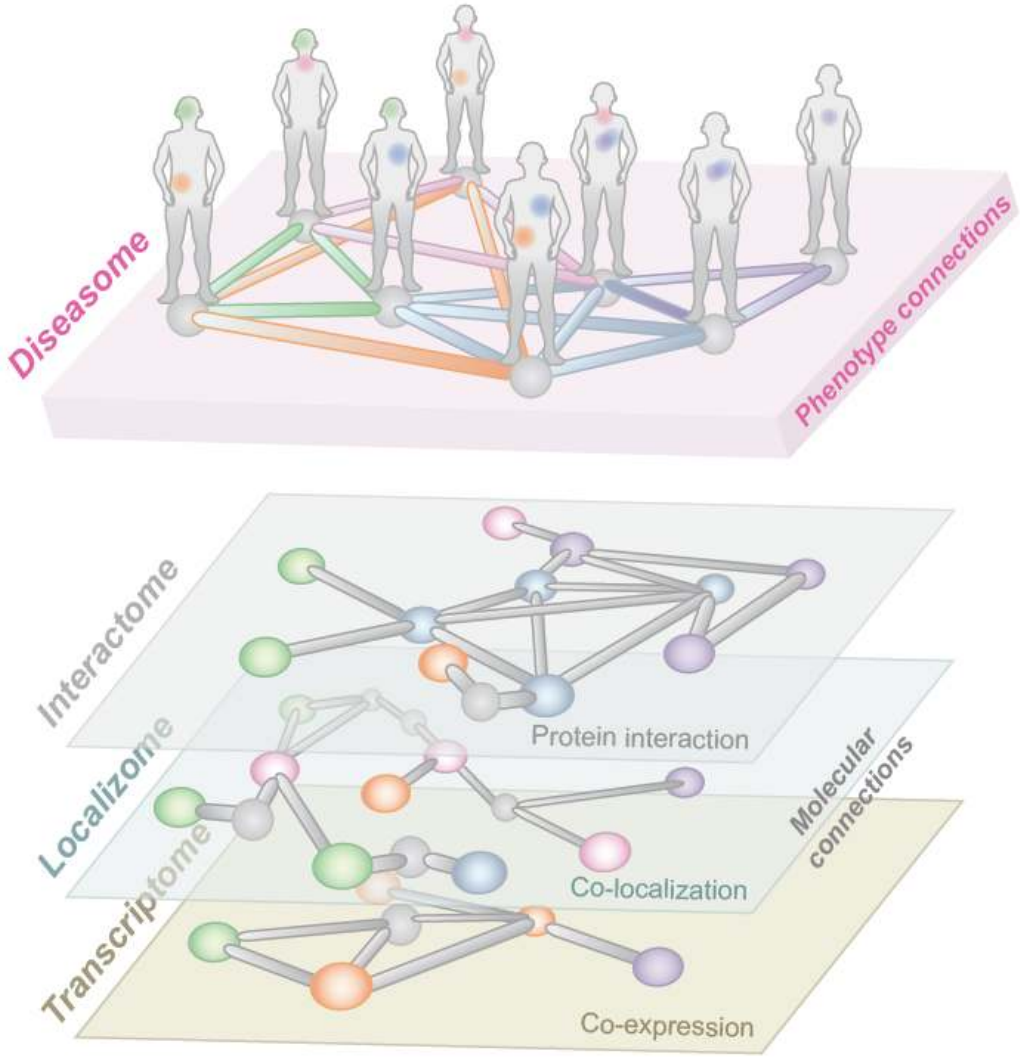


Costanzo et al. The Genetic Landscape of a Cell. Science (2010) vol. 327 (5964) pp. 425
http://www.sciencemag.org/cgi/content/full/327/5964/425

Procedures to connect comorbidity and genetic associations

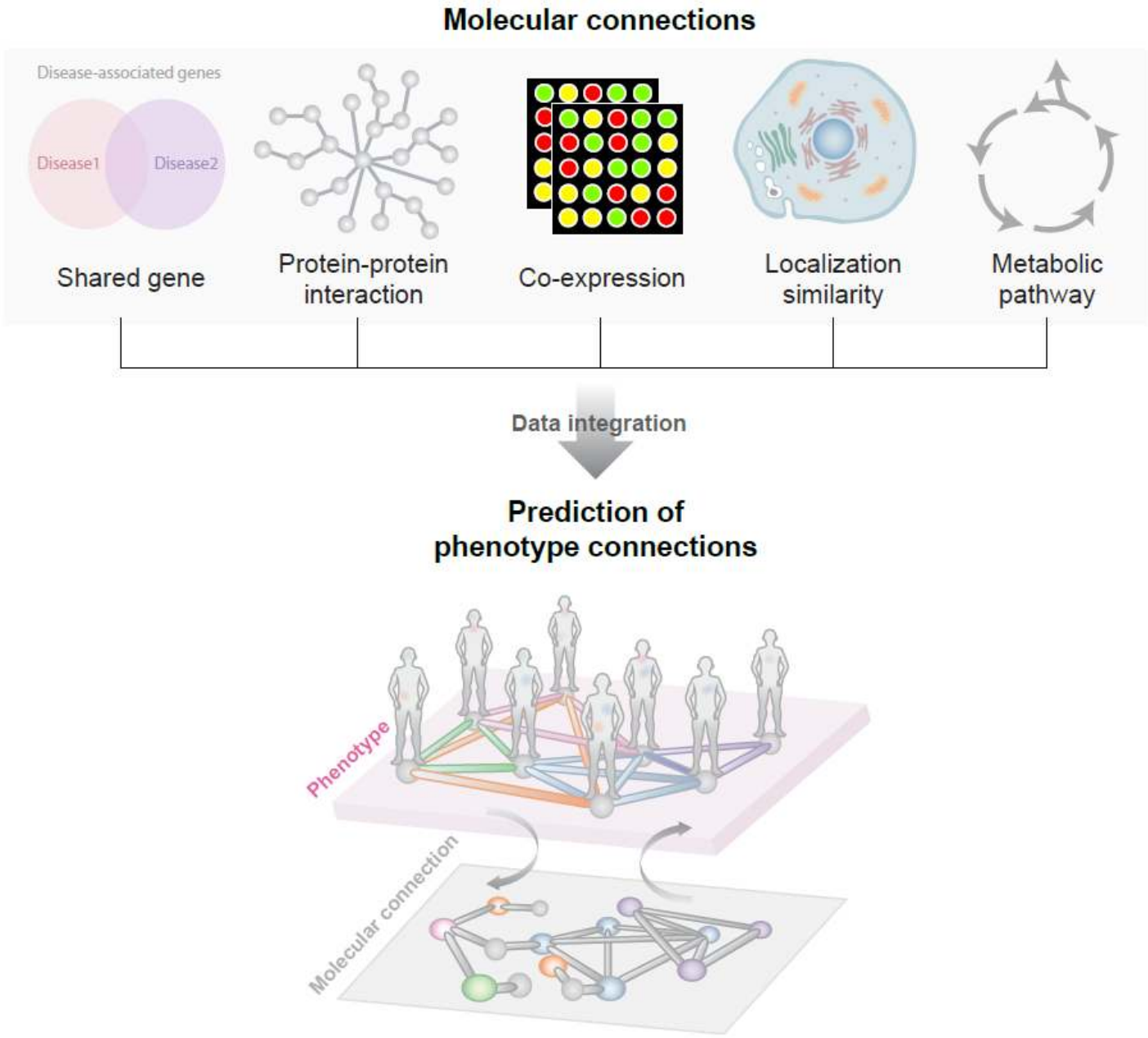


Genotype-phenotype connections



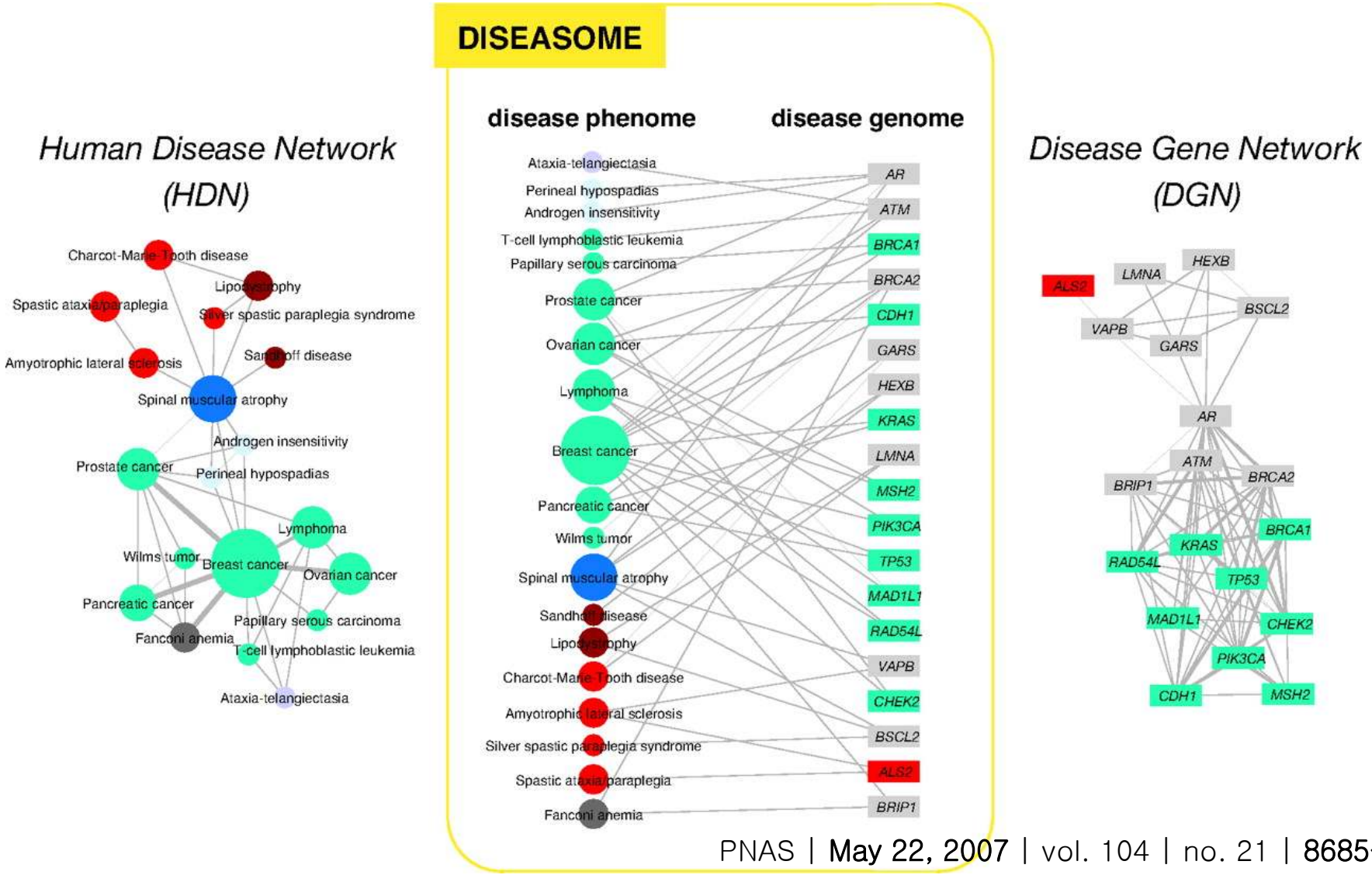
Phenotype connections are triggered by various types of molecular connections

Integrative approach to predict phenotype connections



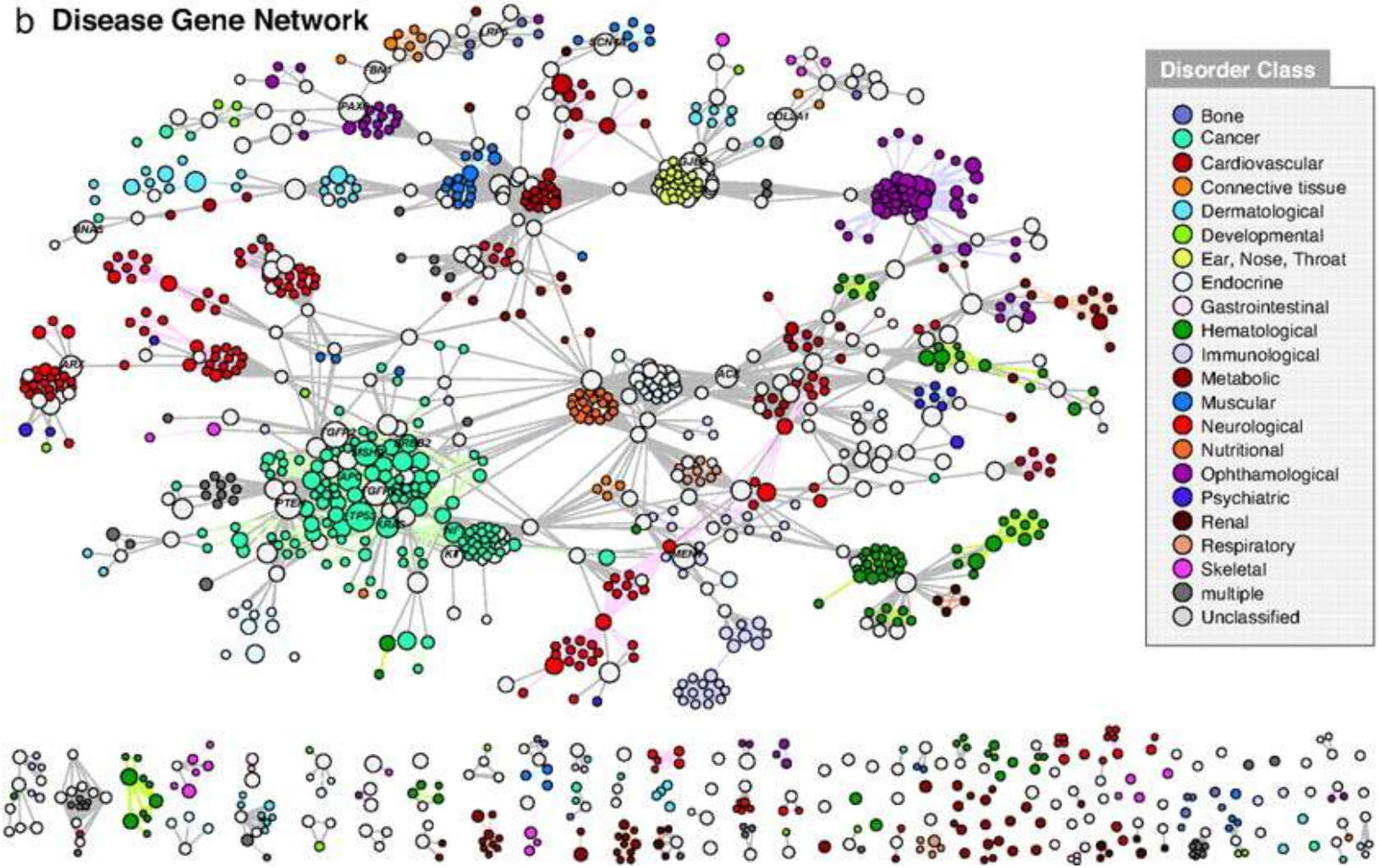
The human disease network

Construction of the diseasome bipartite network

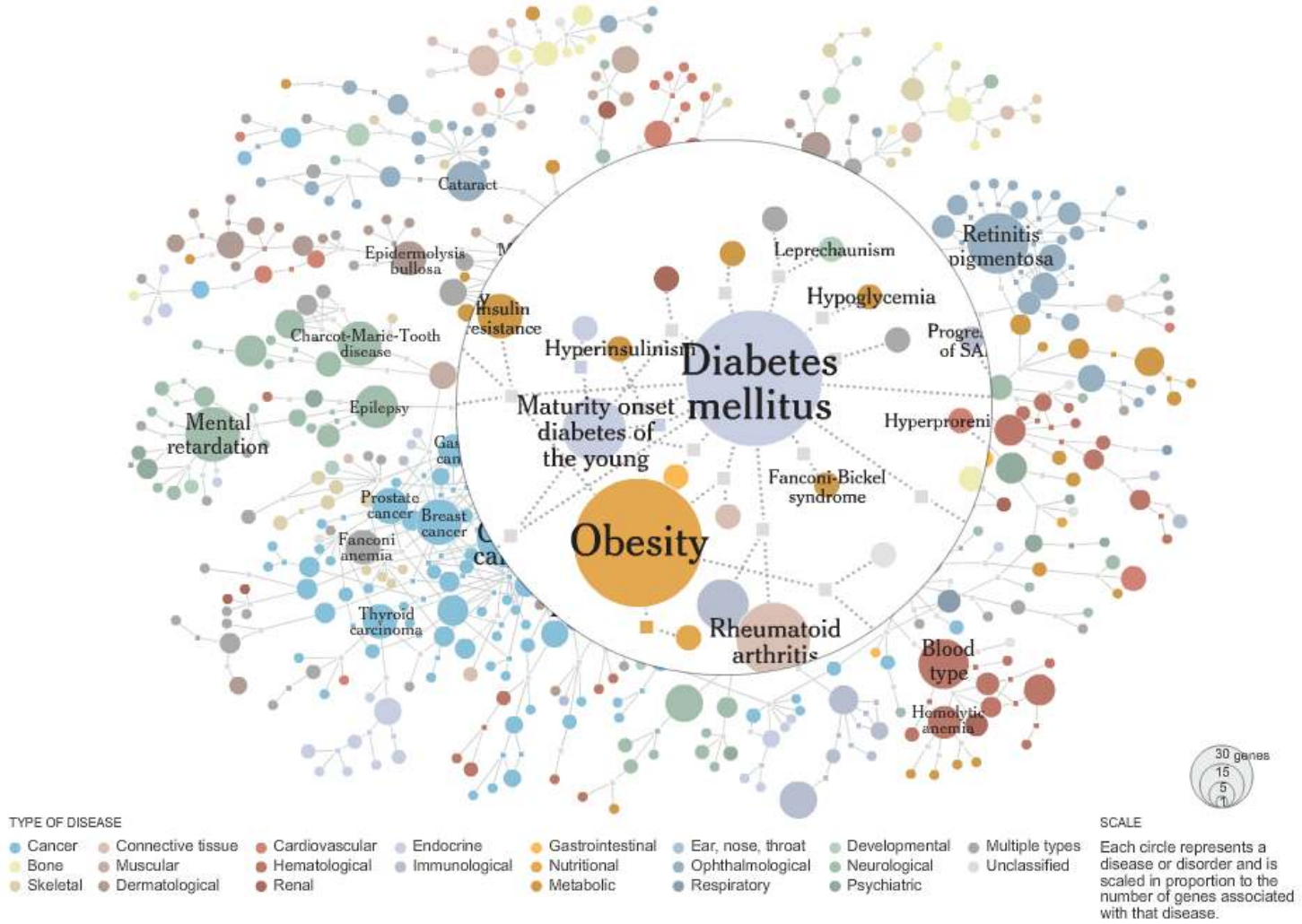


PNAS | May 22, 2007 | vol. 104 | no. 21 | 8685–8690

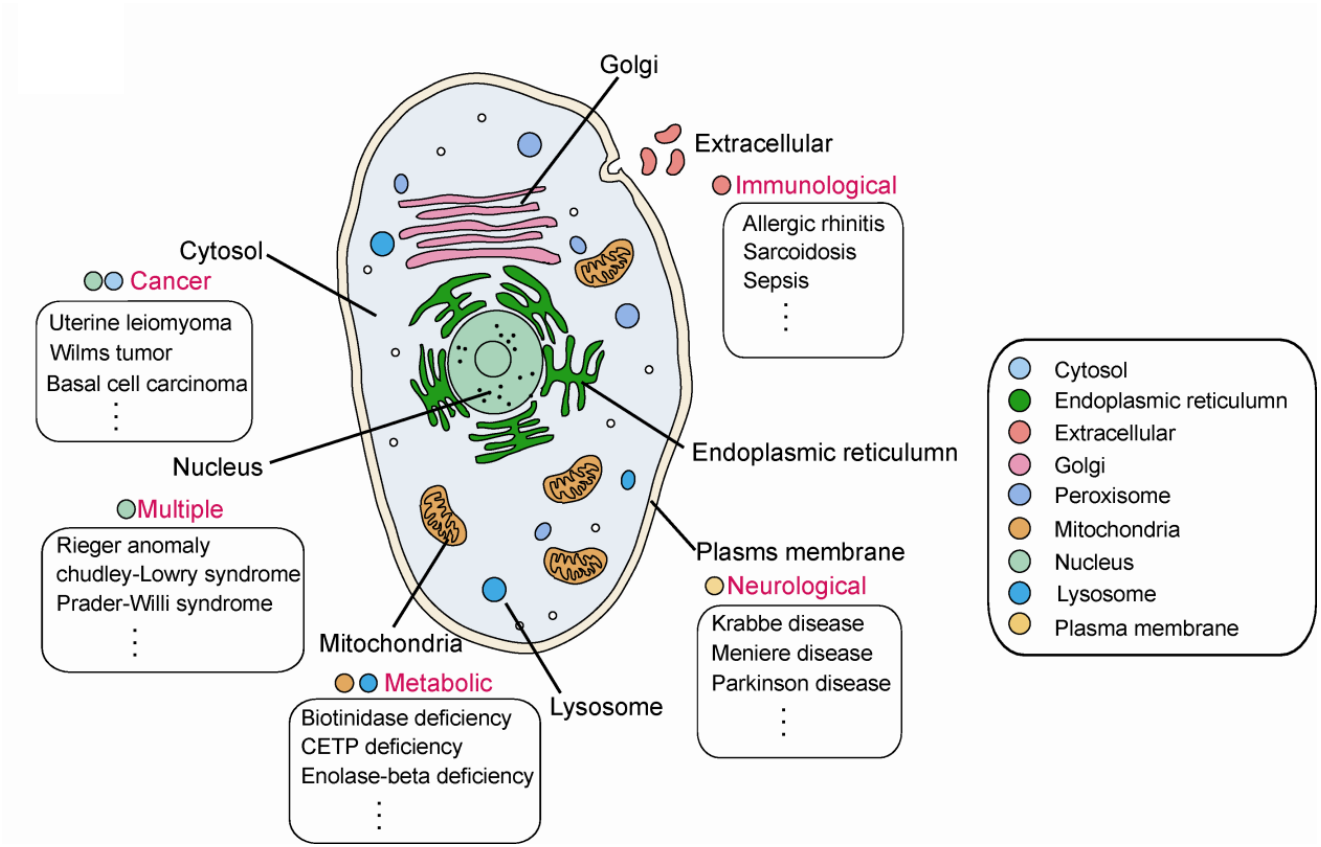
Disease Gene Network



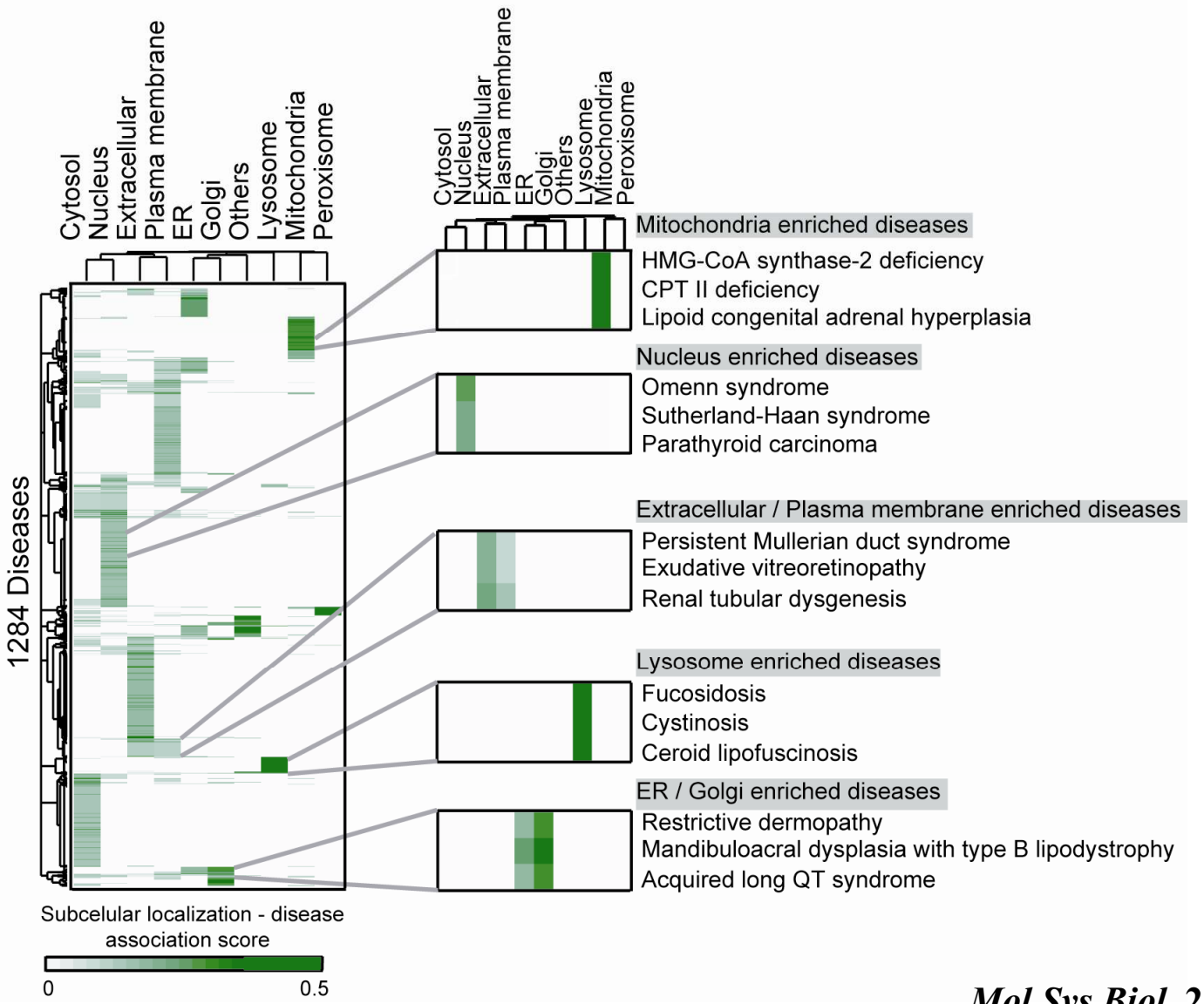
Example: Diabetes in the Human disease network



Protein subcellular localization and Human diseases

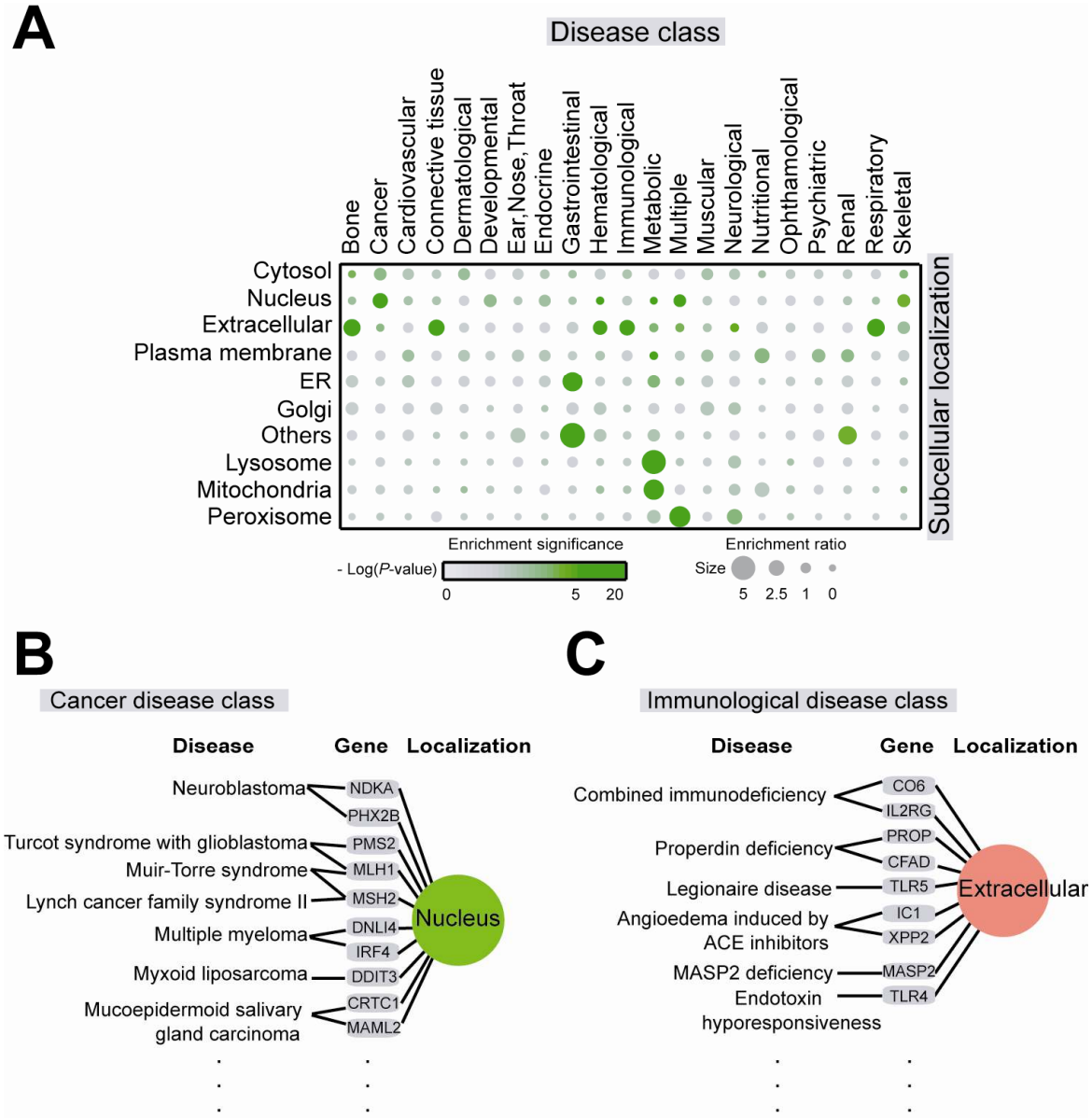


Relationships between disease-associated proteins and their subcellular localizations



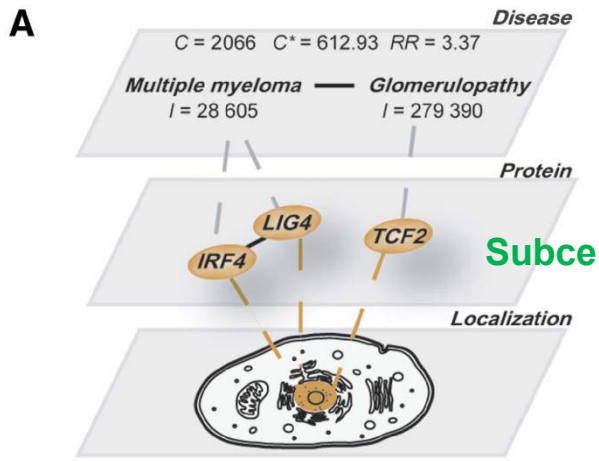
Mol Sys Biol. **2011** 7:494.

Correlation between disease classes and subcellular localizations



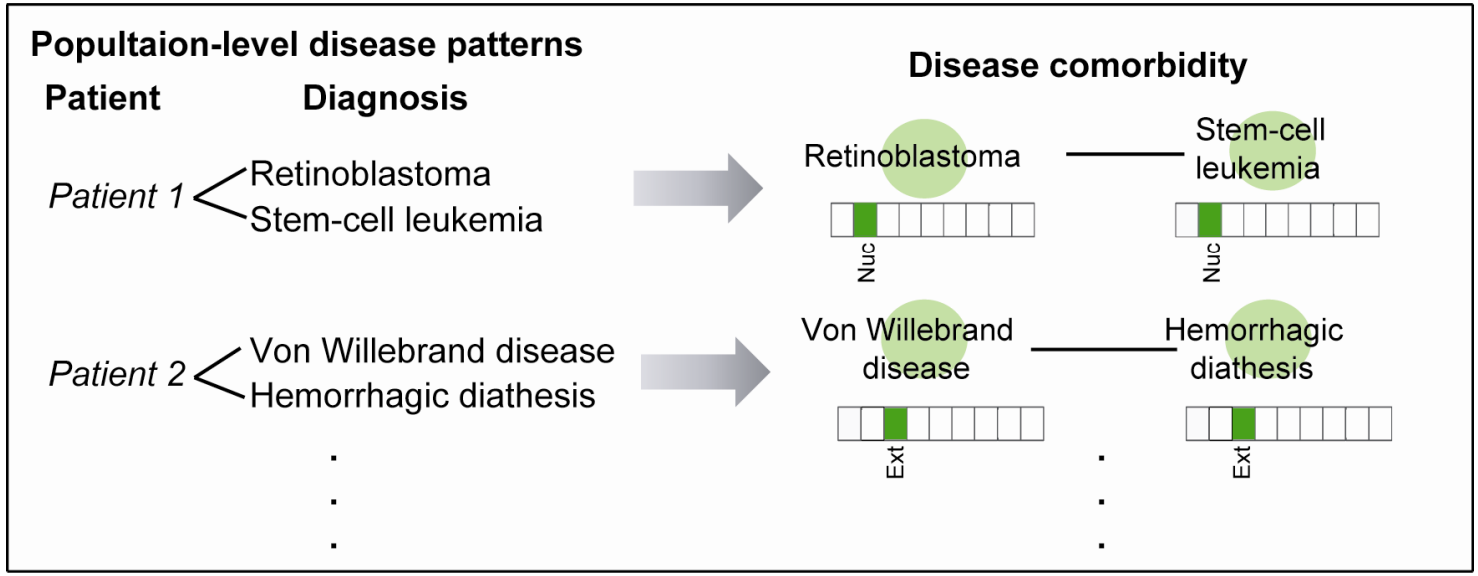
Mol Sys Biol. **2011** 7:494.

The implication of subcellular localization for disease comorbidity

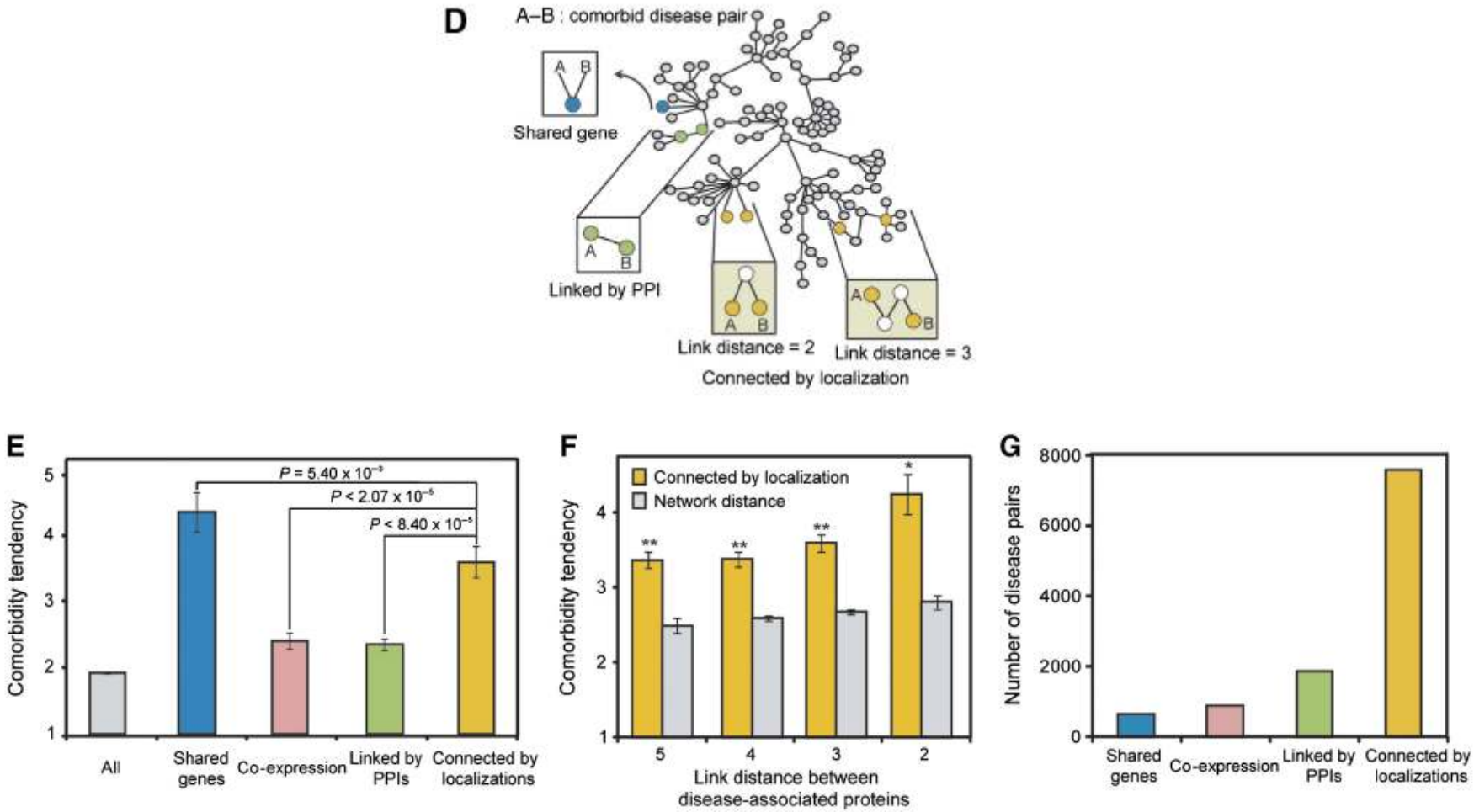


Subcellular localization similarity of human diseases

Subcellular localization similarity of comorbid disease pairs

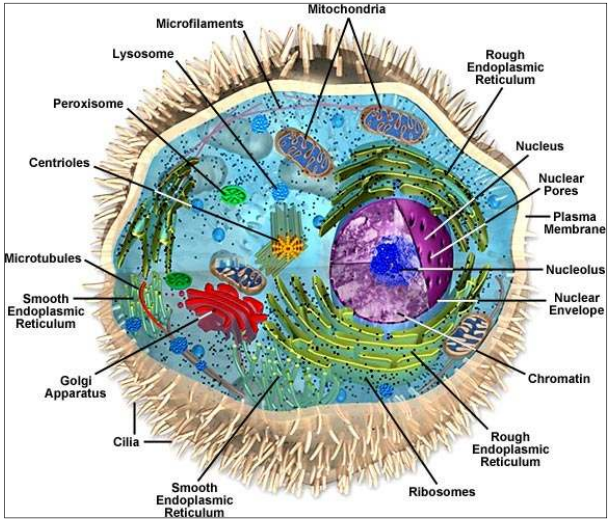


The implication of subcellular localization for disease comorbidity



Mol Sys Biol. **2011** 7:494.

Subcellular localization and human diseases

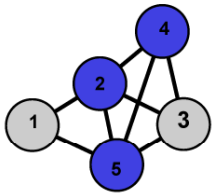


Construction of functional interaction networks through consensus localization predictions of the human proteome.

Park et .al..J. Proteome Res., **2009**, *8* (7), pp 3367–3376

A

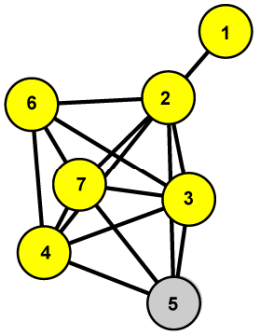
Localization: Plasma membrane
Disease: Basal cell carcinoma



1: GP107_Human
2: PTC1_Human
3: HHIP_Human
4: SMO_Human
5: PTC2_Human

B

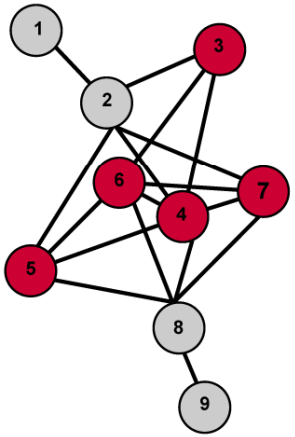
Localization: Cytosol
Disease: Deafness, autosomal dominant



1: MYO3A_Human (Con)
2: WHRN_Human
3: MYO15_Human
4: OMP_Human
5: MYO6_Human
6: MYO7A_Human
7: USH1C_Human (Con)

C

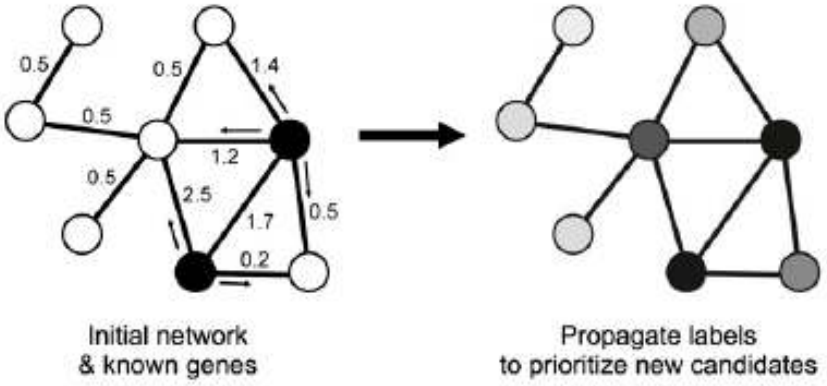
Localization: Nucleus
Disease: Mental retardation

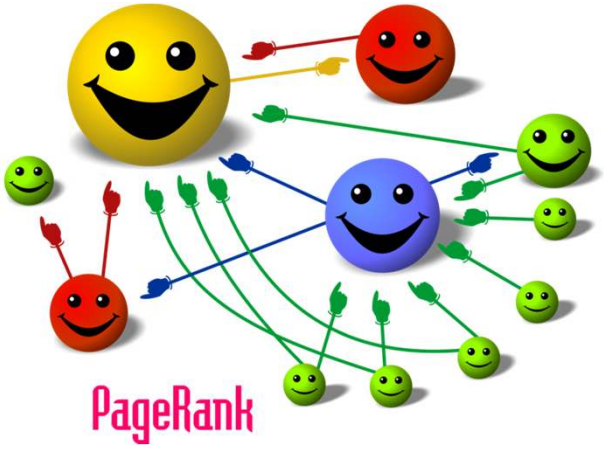


1: VEX2_Human (Con)
2: ARX_Human
3: ZNF81_Human
4: JADIC_Human
5: AFF2_Human (Con)
6: OPHN1_Human
7: ZNF41_Human (Con)
8: ACSL4_Human
9: TMEM9_Human

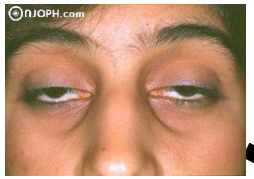
> Protein localization information facilitates the identification of disease associated genes

Network position reveals spatial and functional organization of mitochondrial proteins

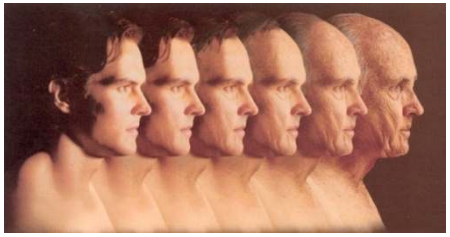




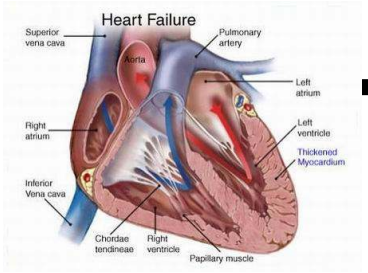
Eye diseases

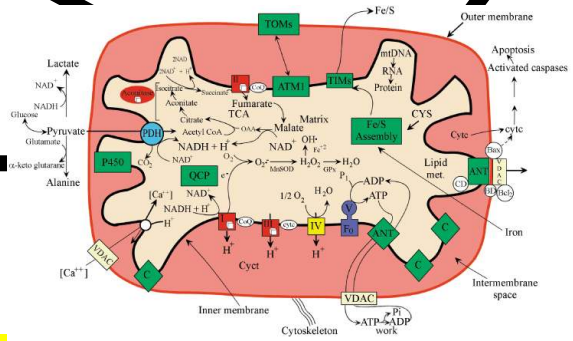


Aging

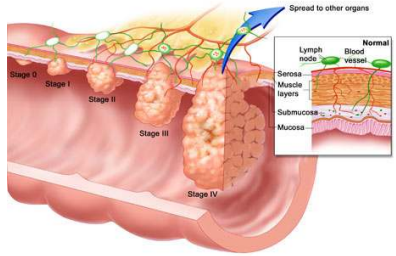


Heart failure



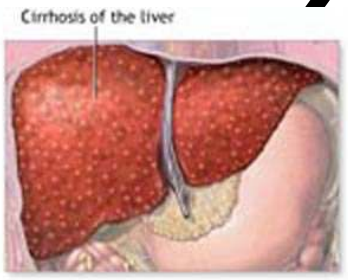


Cancer

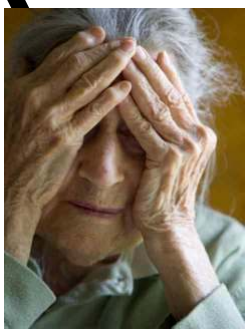


Dysfunction of mitochondria is related over 400 disease phenotypes

Liver failure



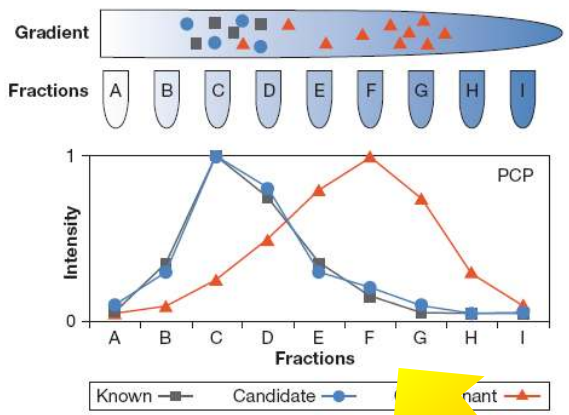
Alzhaimer



PLoS Comput Biol 5(4): e1000374.
http://www.cellsignal.com/reference/pathway/Apoptosis_Mitochondrial.html

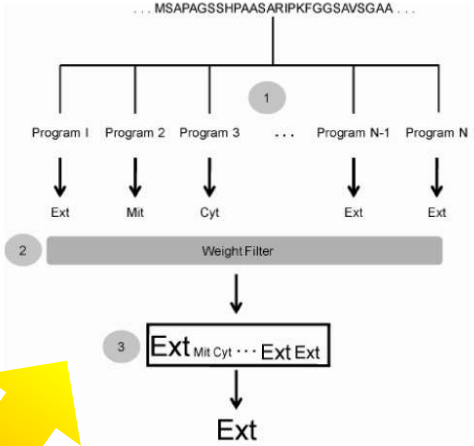
Extensive experiments and bioinformatics approaches have been applied to identify mitochondrial proteome

Experiments

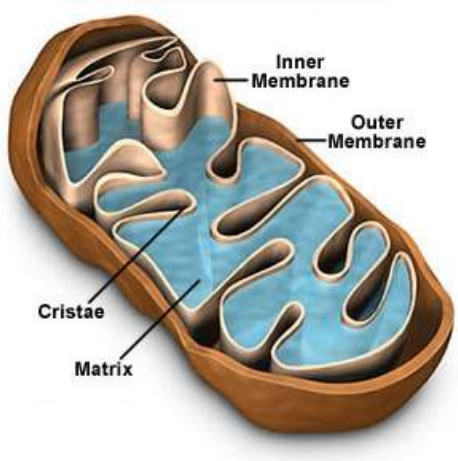


EMBO reports **7**, 9, 874–879 (2006)
Organellar proteomics: turning inv ies into insights
Jens S Andersen[1] & Matthias Mann[2]

Bioinformatics

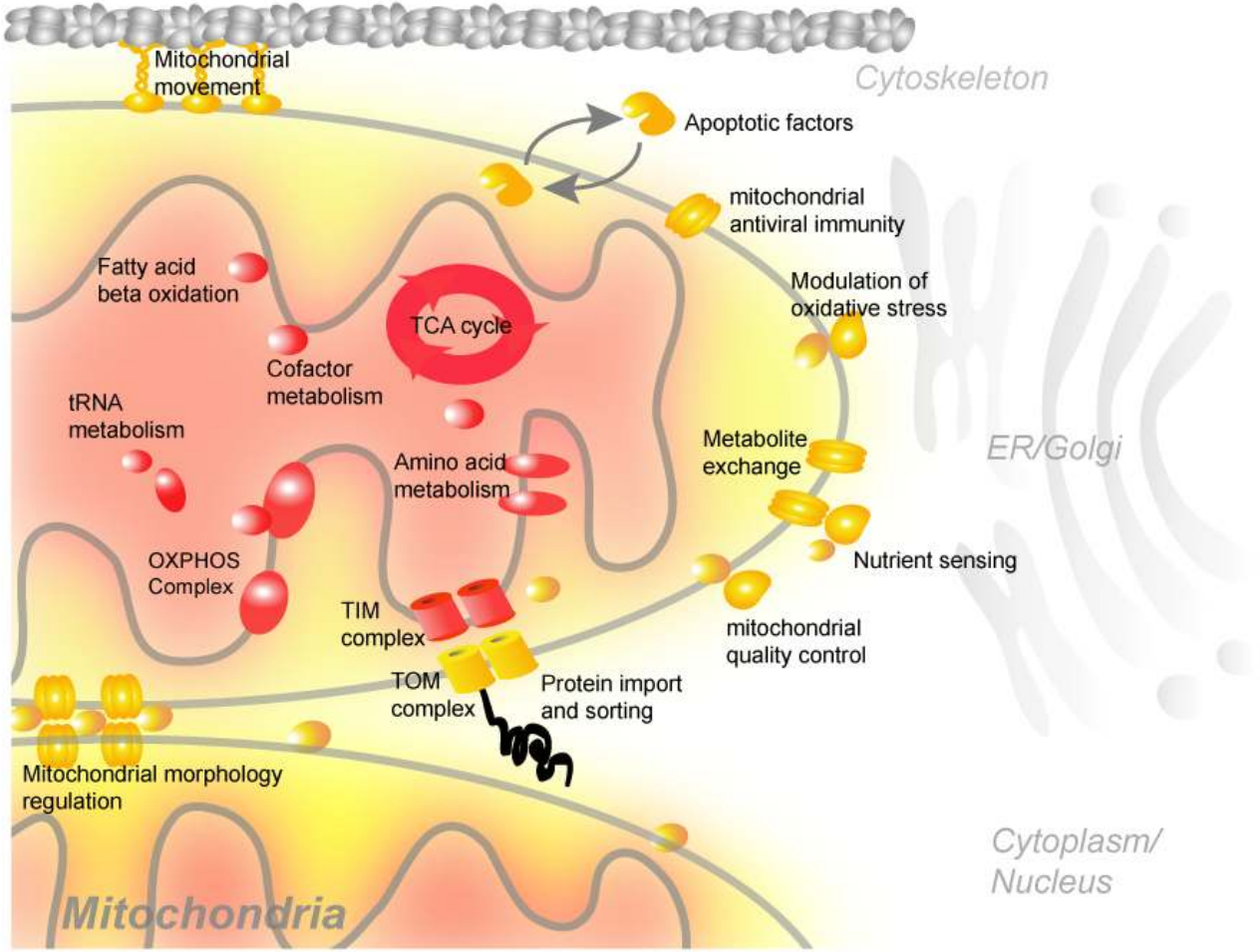


Park, S., Yang, J.S., Jang, S.K. and Kim, S. (2009)
Construction of functional interaction networks through consensus localization predictions of the human proteome, *J Proteome Res*, ***8, 3367-3376.***

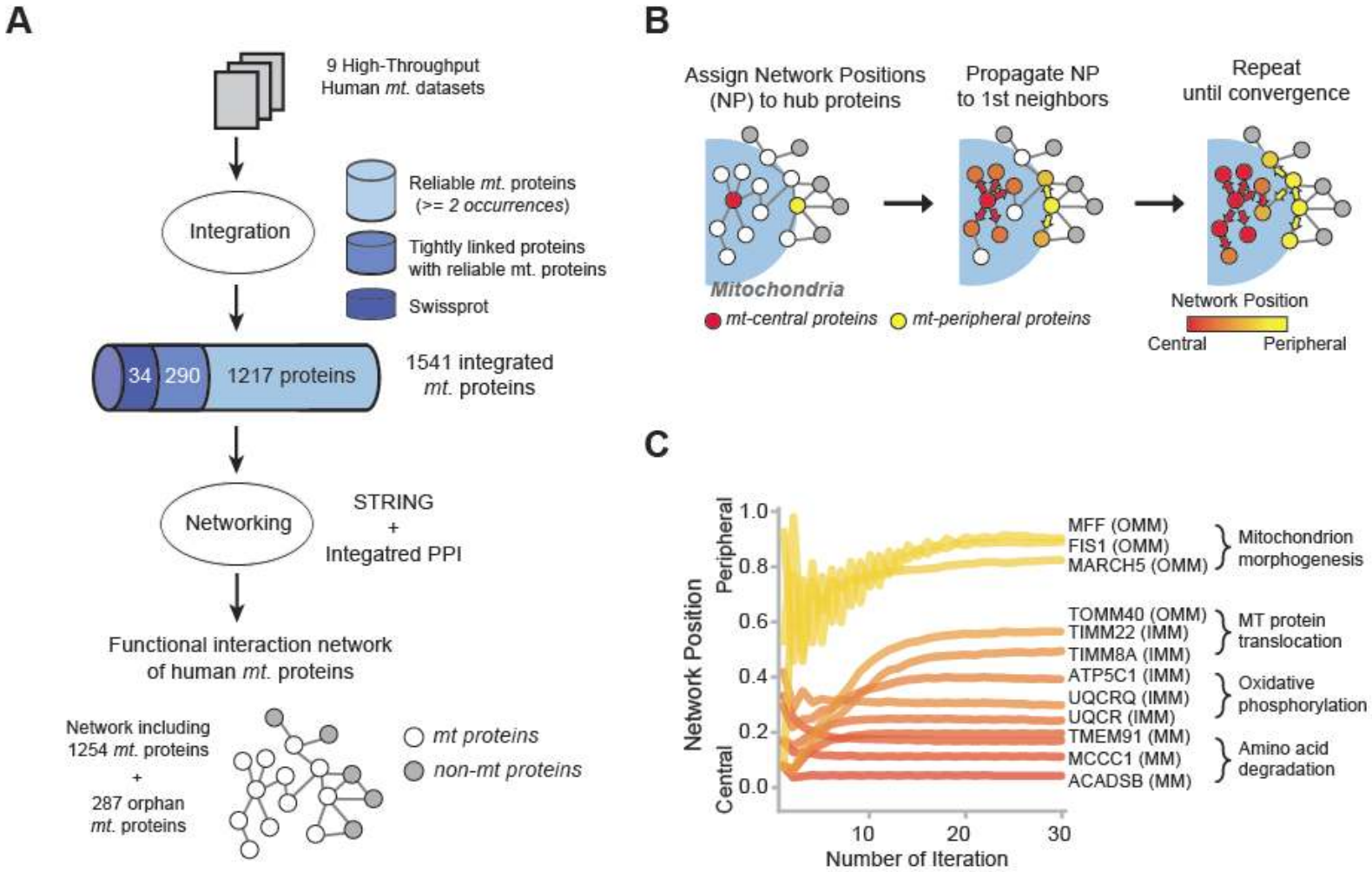


Identification of mitochondrial proteins

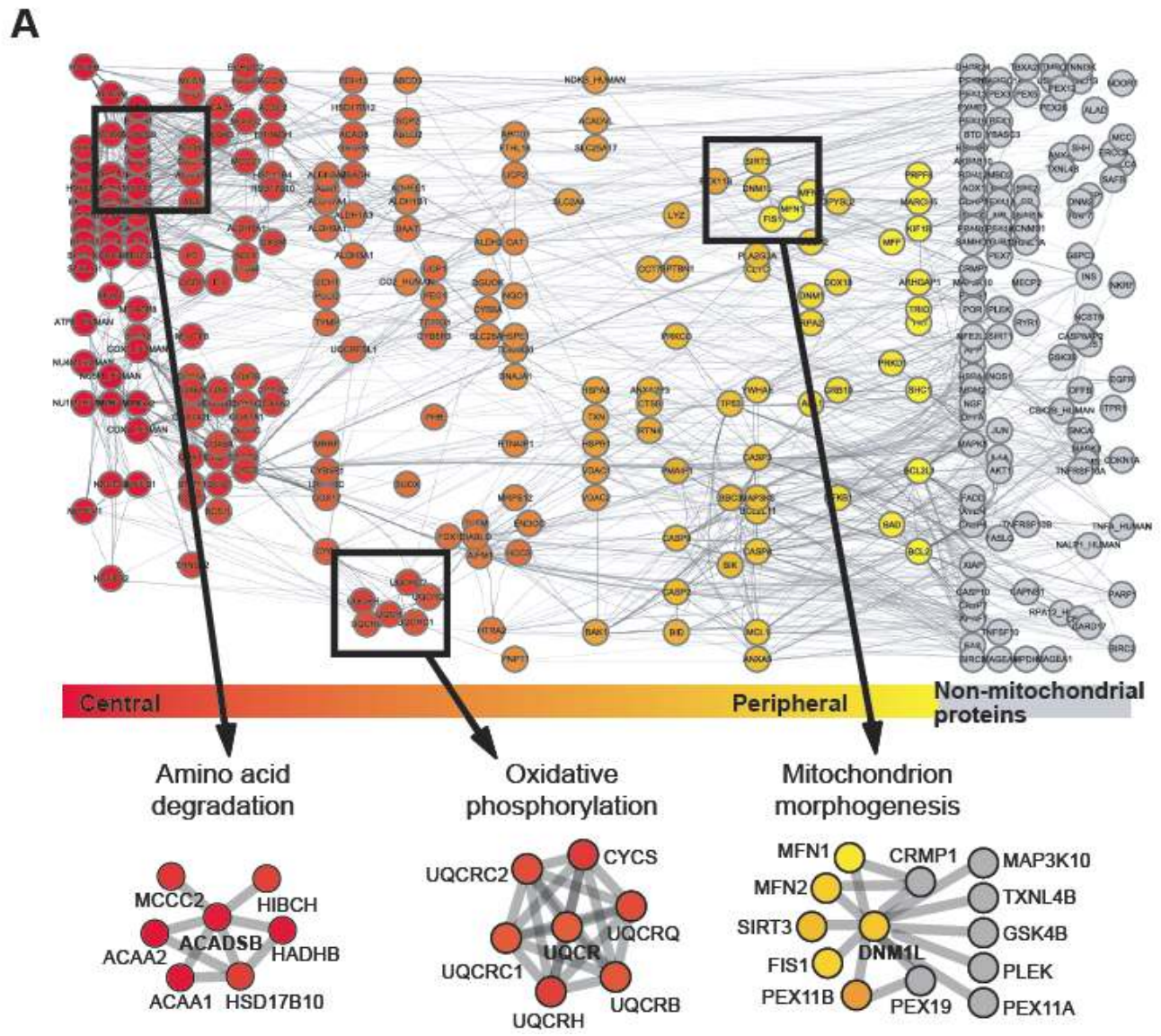
Identifying spatial organization of mitochondrial proteins provide key clues for functions



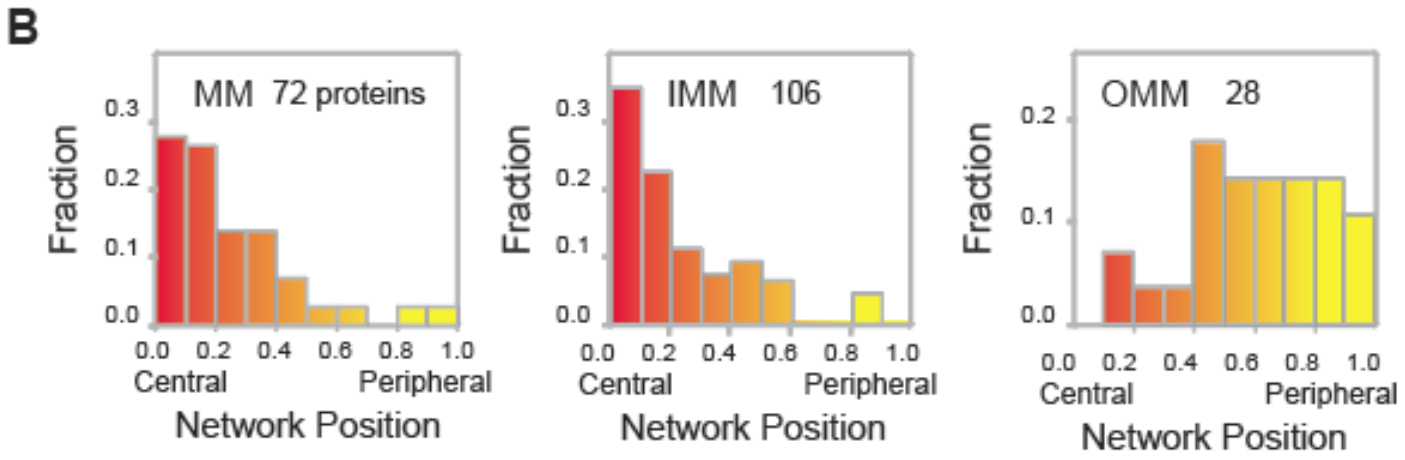
Assigning network position of mitochondrial proteins in functional interaction network



Network position reflects spatial organization of mitochondrial proteins



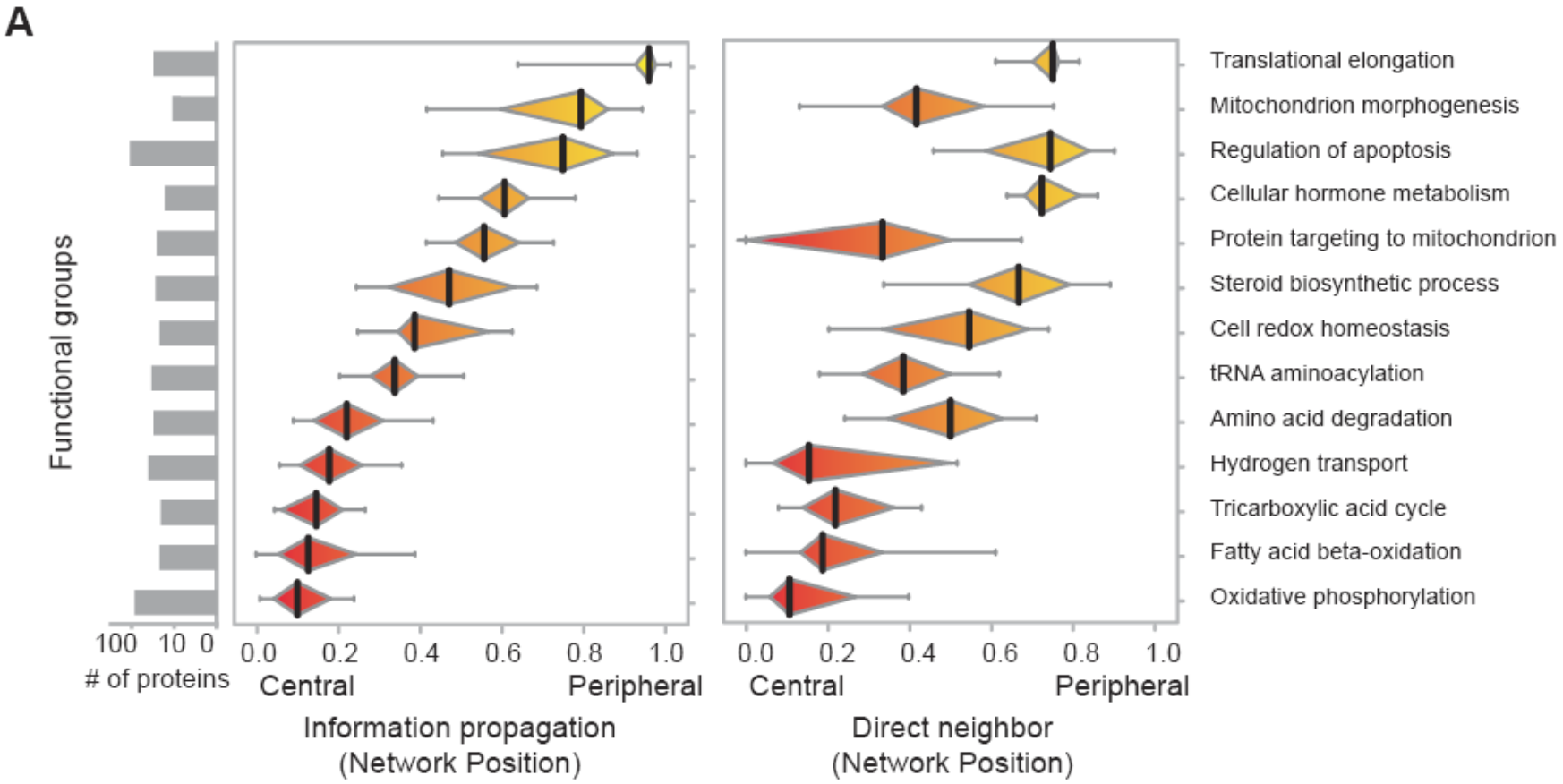
Network position reflects spatial organization of mitochondrial proteins



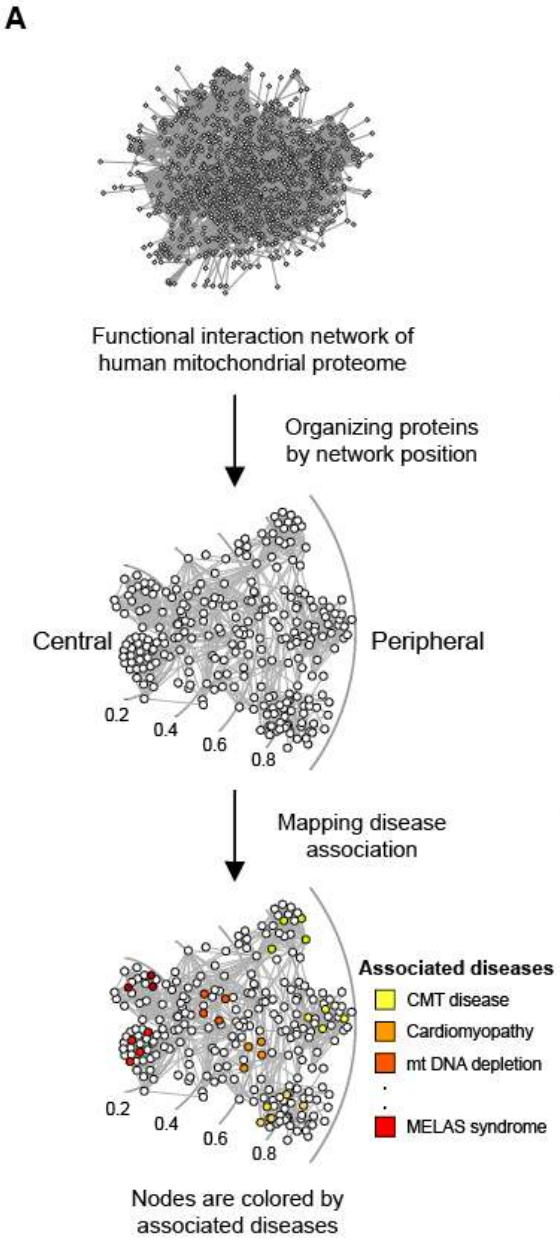
Network position reflects spatial organization of mitochondrial proteins

Gene Symbol	Sub-mitochondrial compartments	Network position	Prediction result	Related Functions
NLRX1	**OMM**	**0.83**	**O**	**Antiviral signaling**
TOM6	**OMM**	**0.88**	**O**	**Preprotein translocase complex**
MUL1	**OMM**	**0.83**	**O**	**Control of mt morphology**
MFF	**OMM**	**0.79**	**O**	**Mitochondrial fission**
SNN	**OMM**	**0.69**	**O**	**Response to abiotic stimulus**
PINK1	**OMM**	**0.65**	**O**	**Protect against mt dysfunction**
PGAM5	**OMM**	**0.63**	**O**	**Regulator of mt dynamics**
UBP30	**OMM**	**0.55**	**O**	**Maintenance of mt morphology**
EXOG	IMM	0.81	X	Endo/exonuclease
LETM1	IMM	0.8	X	Mitochondrial tubular networks and cristae
TPC	**IMM**	**0.41**	**O**	**Uptake ThPP into mitochondria**
COQ7	**IMM**	**0.32**	**O**	**Ubiquinone biosynthesis**
CT007	**IMM**	**0.31**	**O**	**Putative methyltransferase**
COQ4	**IMM**	**0.23**	**O**	**Ubiquinone biosynthesis**
COX8A	**IMM**	**0.17**	**O**	**Cytochrome c oxidase**
COX8C	**IMM**	**0.16**	**O**	**Cytochrome c oxidase**
SIRT4	MM	0.66	X	GLUD1 enzyme activity, Insulin secretion
DHB8	**MM**	**0.43**	**O**	**Estrogen biosynthesis**
CLPP	**MM**	**0.39**	**O**	**Clp protease**
MIPEP	**MM**	**0.38**	**O**	**Mitochondrial intermediate peptidase**
MCCB	**MM**	**0.1**	**O**	**Leucine degradation**
CBR4	**MM**	**0.1**	**O**	**Biosynthesis of fatty acids**
SCOT1	**MM**	**0.05**	**O**	**Ketone body catabolism**
ACS2L	**MM**	**0.01**	**O**	**Maintaining normal body temperature**

Network position reflects functional organization of mitochondrial proteins

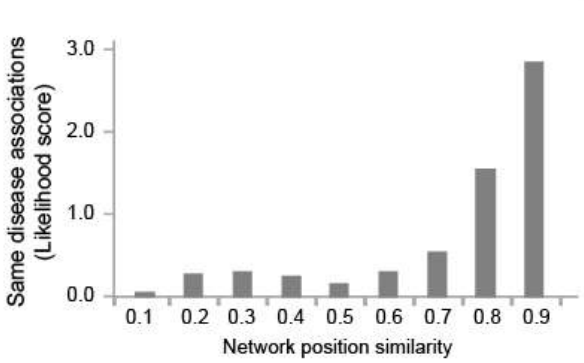


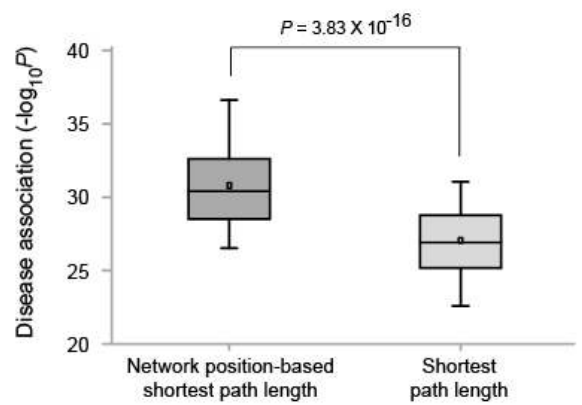
Network positions are similar between same disease associated protein pairs



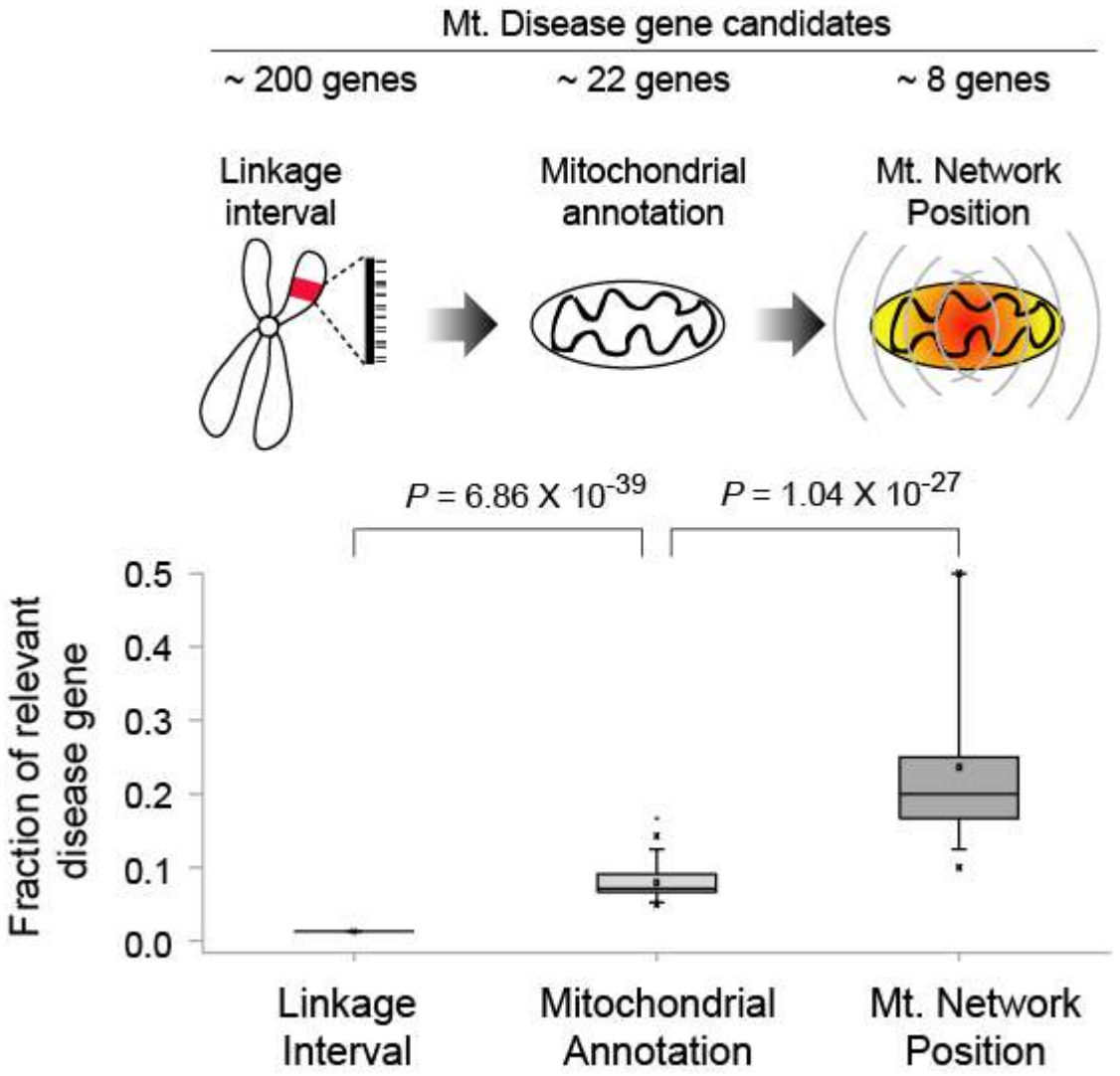
B

Associated disease	Network position ± SD	# of associated genes
MELAS syndrome	0.01 ± 0.01	5
Pyruvate dehydrogenase deficiency	0.03 ± 0.01	5
Leber hereditary optic neuropathy	0.03 ± 0.04	10
Leigh syndrome	0.11 ± 0.09	21
NADH-CoQ reductase deficiency	0.13 ± 0.17	14
Fatal infantile cytochrome C oxidase deficiency	0.14 ± 0.02	5
Nonsyndromic genetic deafness	0.33 ± 0.30	6
Mitochondrial DNA depletion syndrome	0.34 ± 0.08	5
Cardiomyopathy, familial dilated	0.75 ± 0.13	7
Autosomal dominant Charcot-Marie-Tooth disease, type 2	0.79 ± 0.17	5





Network position can help to find mitochondrial disease candidates

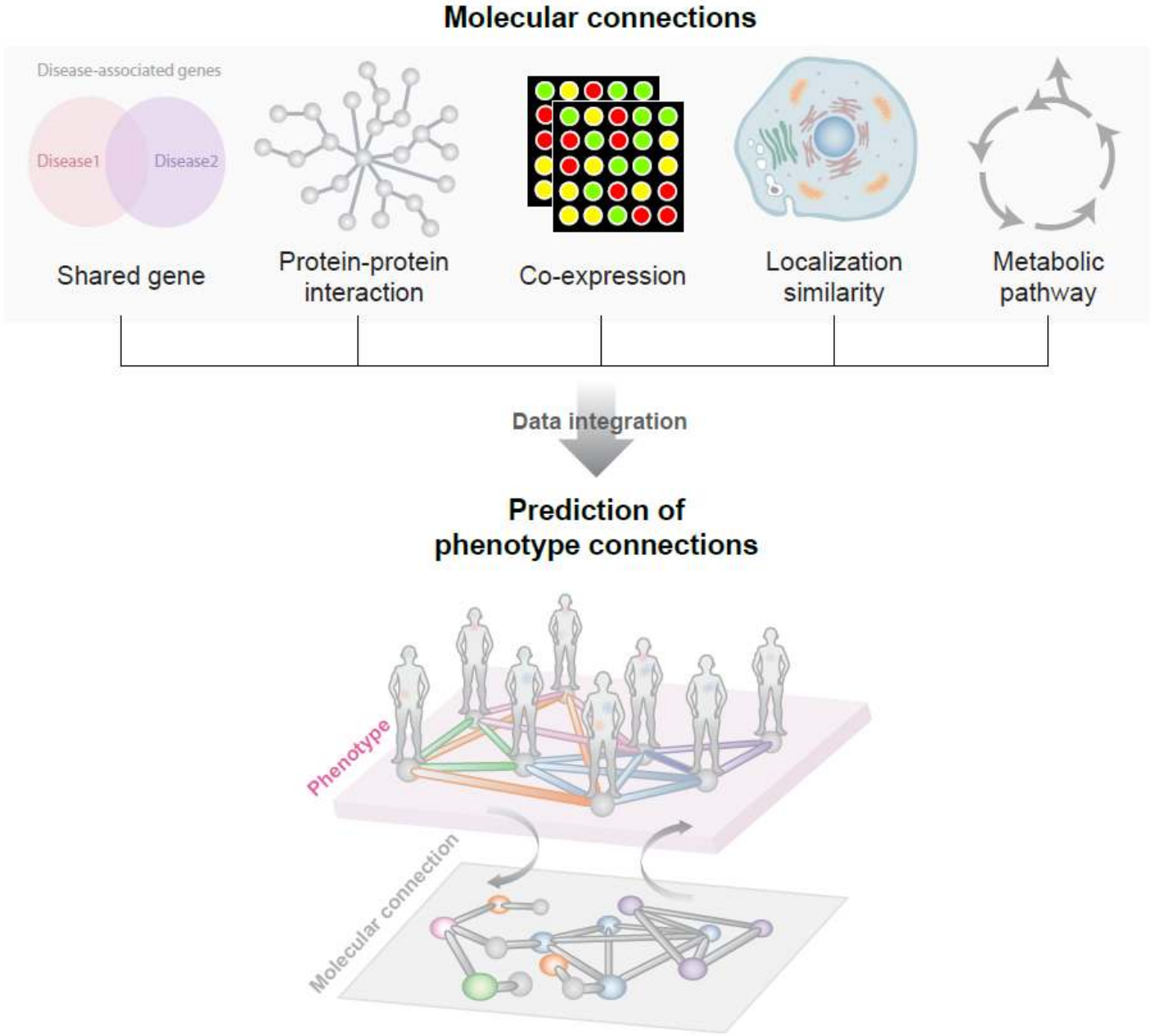


Network position can help to find mitochondrial disease candidates

Disease (OMIM)	Linkage region	Linkage Interval	Mitochondrial Annotation	Mt. Network Position	Disease candidates
Hepatic mtDNA depletion	D2S2373– D2S2259	186	17	2	CAD, MPV17
Cardiomyopathy, familial dilated. (FDC)	10q21-10q23	313	43	18	PSAP, RPS24, ACTA2, CYP26A1, MARCH5, PPA1, IDE, ANXA11, IFIT3, SLC25A16, SUPV3L1, PHYHIPL, NDST2, AIFM2, CYP2C19, MINPP1, ARID5B, LDB3
Cardiomyopathy, familial dilated. (FDC)	9q13-9q22	214	22	14	TDRD7, HSPBL2, PRKACG, RFK, VPS13A, ANXA1, C9orf89, SECISBP2, UBQLN1, NTRK2, NCBP1, NANS, HNRNPK, IARS
Charcot-Marie-Tooth disease type 2 (CMT2F)	7q11-7q21	256	20	4	CYP51A1, HSPB1, ELN, GTPBP10
Charcot-Marie-Tooth disease type 2 (CMT2L)	D12S366-D12S1611	107	17	11	DIABLO, TRIAP1, COQ5, MSI1, RPS2P5, RAB35, HSPB8, POP5, CLIP1, PEBP1, PLA2G1B
mtDNA depletion syndrome (MDS)	2p13	125	18	3	HK2, SPR, DGUOK

Underlined genes in the disease candidates are known to be associated with mitochondrial diseases

Integrative approaches for network medicine of human diseases



Structural Bioinformatics Laboratory
Pohang University of Science and Technology

Acknowledgement

SBI lab

Jou-hyun Jeon
Jae-seong Yang
Solip Park
Yonghwan Choi
Yoonsup Choi
Jinho Kim
HyunJun Nam
JiHye Hwang
Inhae Kim
Youngeun Shin
Sung gyu Han