Jornadas PhenUMA

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SESIÓN IV:
Integration of Phenotypic and Functional Networks

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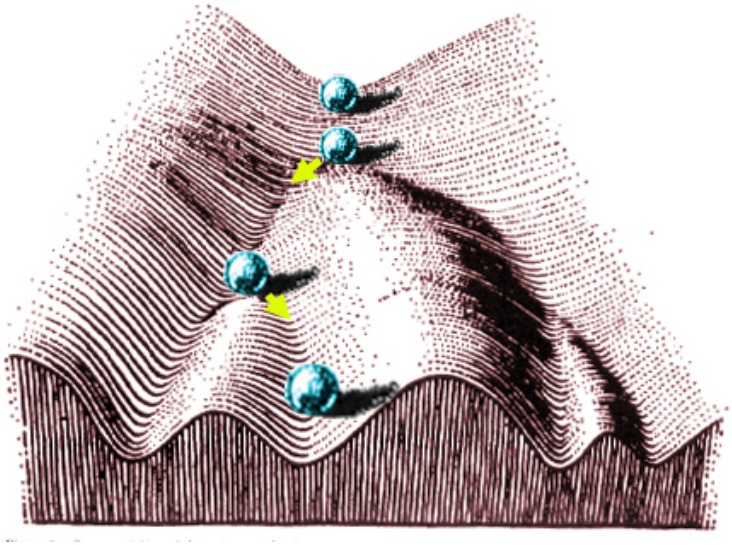
Biological robustness

*"Biological systems, from macromolecules to whole organisms, are **robust** if they continue to function, survive, or reproduce when faced with mutations, environmental change, and internal noise"*

Identify how biological systems lose robustness

Landscape Metaphor:
Canalization in development biology

Rolling balls down-hill

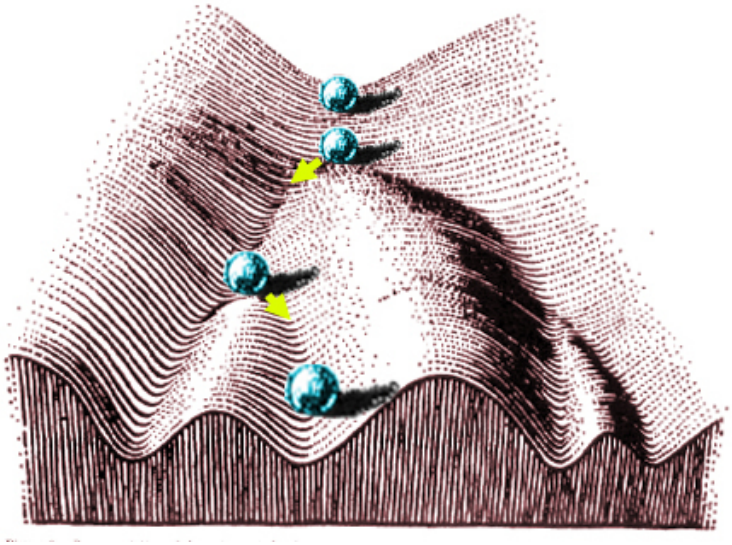


1. Genetic
2. Environmental
3. Stochastic
   (noise or random events)

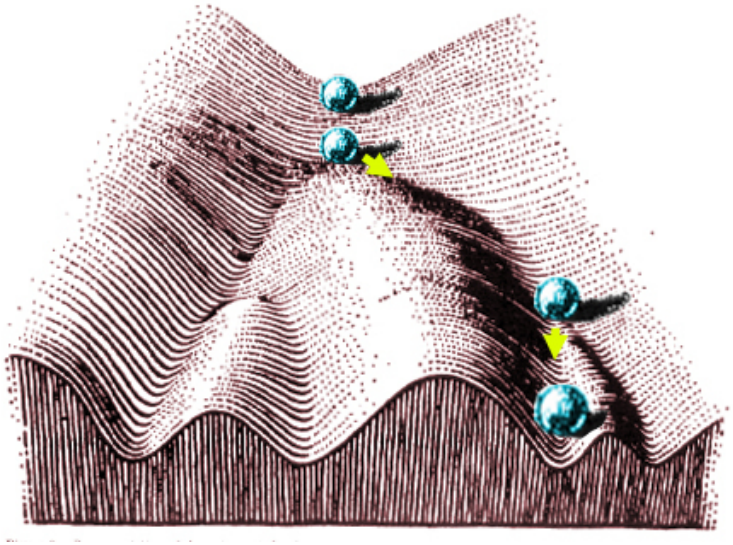
Conrad Hal Waddington

Landscape Metaphor:
Robustness for phenotypic variability

Wild type

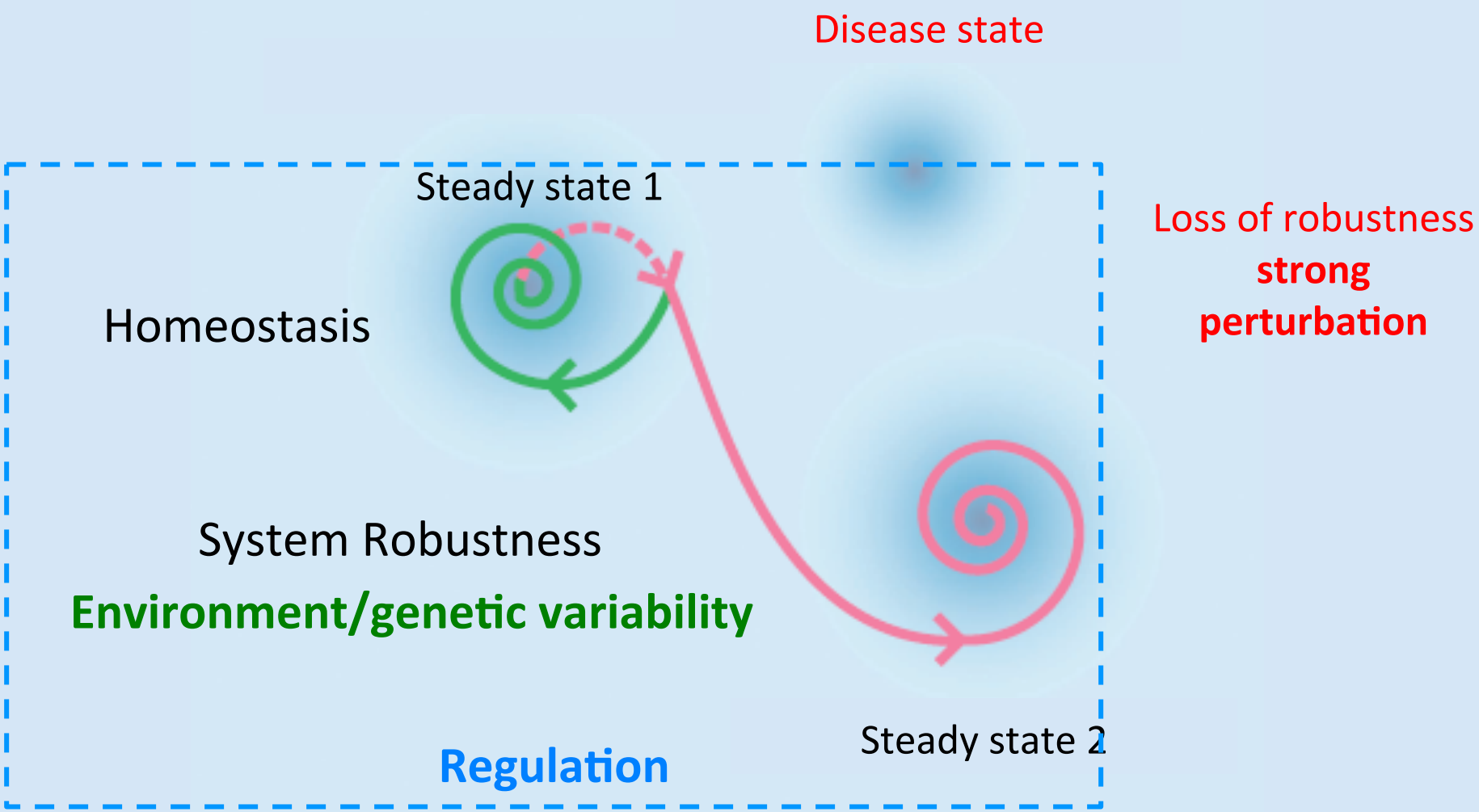


Disease state

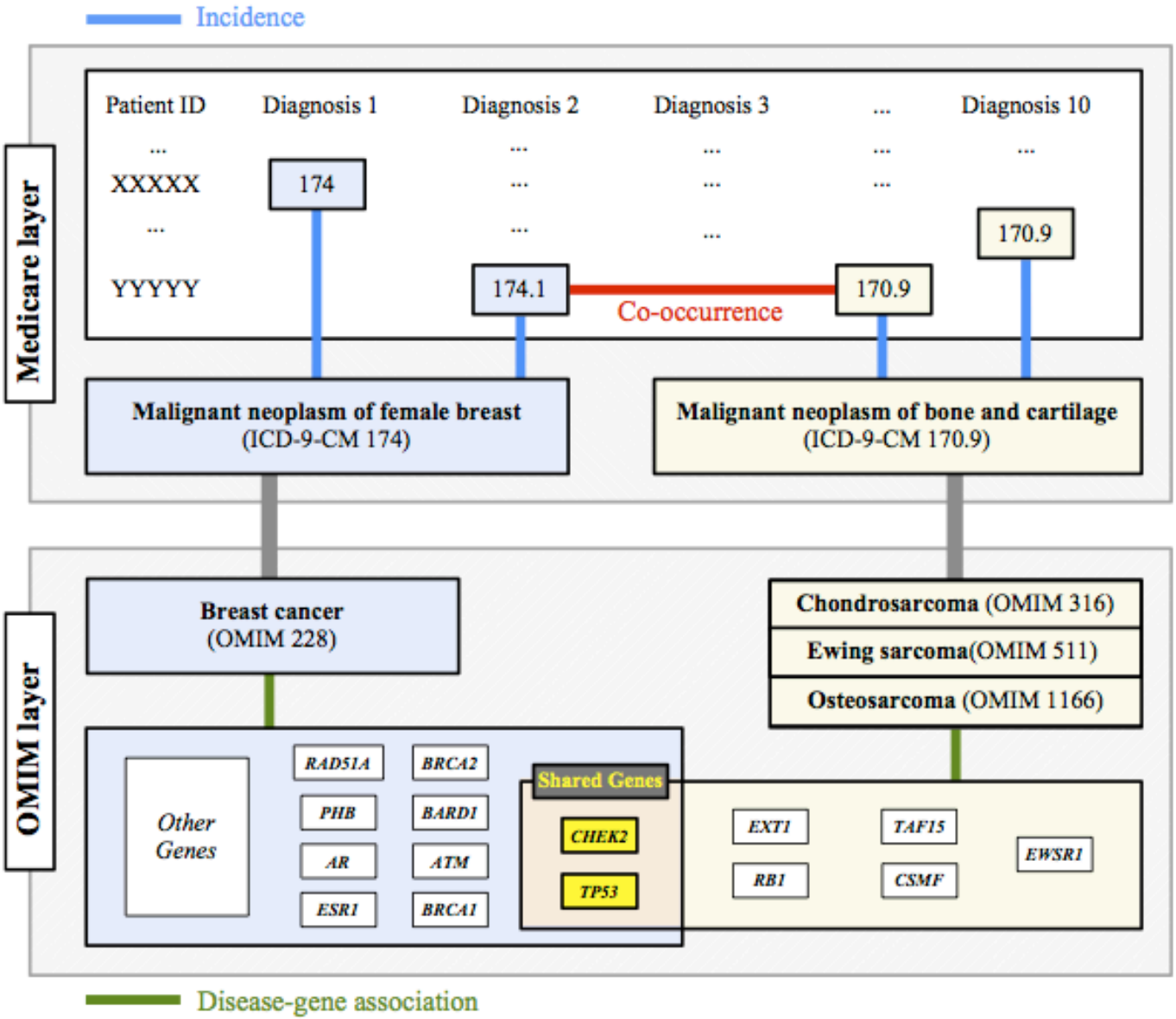


Conrad Hal Waddington

Loss of robustness induces pathogenesis



COMORBIDITY



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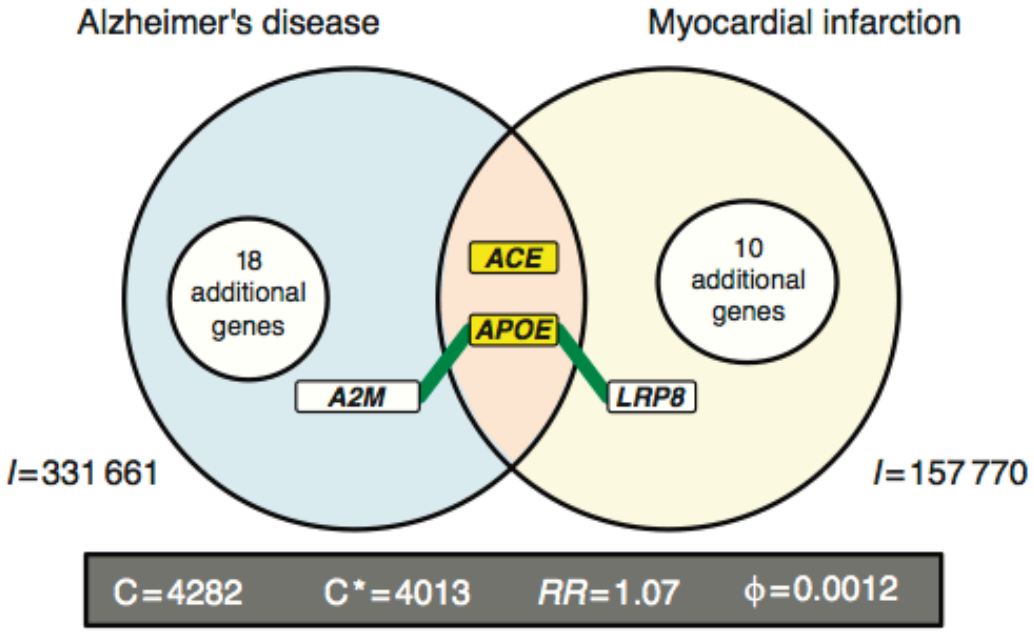
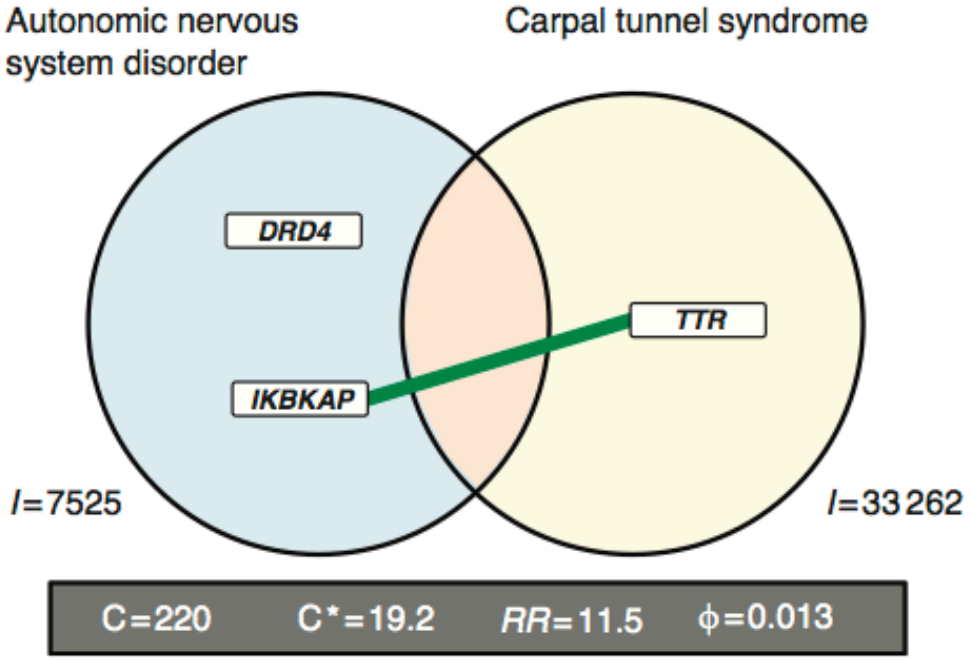


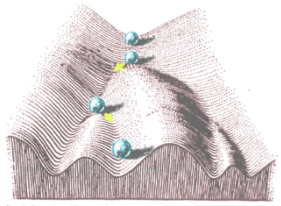


Starting point

- Most genetic influences on a trait/phenotype are usually unknown
- Phenotypic variation is not just due to genetics.

1. **It is NOT necessary detailed mechanistic models** of a biological system in order to predict phenotypic variation, **pragmatic statistical approaches may suffice (Genotype combinations studies)**.

2. **Natural (biological) networks evolved to be robust** to genetic, environmental and stochastic perturbations. GOOD level of abstraction, less precision



Sources of information

1. Genetic diseases
2. Pathological Phenotypes variability
3. Functional interactions between genes

"All of this data can be modeled in networks"

OPEN ACCESS Freely available online

PLOS ONE

Global Analysis of the Human Pathophenotypic Similarity Gene Network Merges Disease Module Components

Armando Reyes-Palomares[1,2], Rocío Rodríguez-López[1,2], Juan A. G. Ranea[1,2], Francisca Sánchez Jiménez[1,2], Miguel Angel Medina[1,2]*

1 Department of Molecular Biology and Biochemistry, Faculty of Sciences, University of Málaga, Málaga, Spain, **2** CIBER de Enfermedades Raras (CIBERER), Málaga, Spain

Databases

OMIM
Online Mendelian Inheritance in Man
Johns Hopkins University

www.omim.org

- Dr. Victor A. McKusick
- Repository of studies about clinical features and molecular genetics

Genetic disorders:	**3.486**
Mutated genes:	**2.794**
All diseases:	**7.263**

orphanet

www.orpha.net

- Focused on low prevalence diseases.
- Originally enriched by OMIM diseases
- Actively reviewed by clinical experts

Genetic disorders:	**2.125**
Mutated genes:	**2.331**
All diseases:	**5.954**

Many cases we know the gene but not the molecular etiology

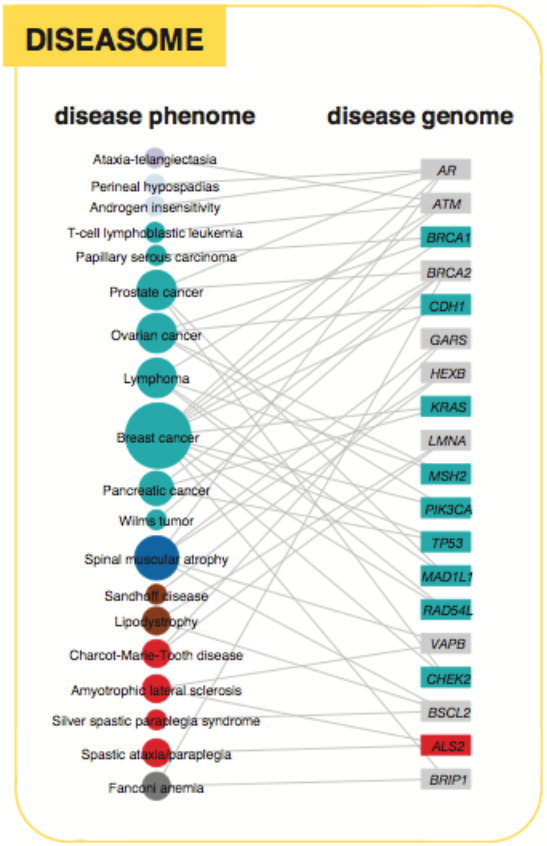
Databases 2 Diseasomes

OMIM Online Mendelian Inheritance in Man — Johns Hopkins University

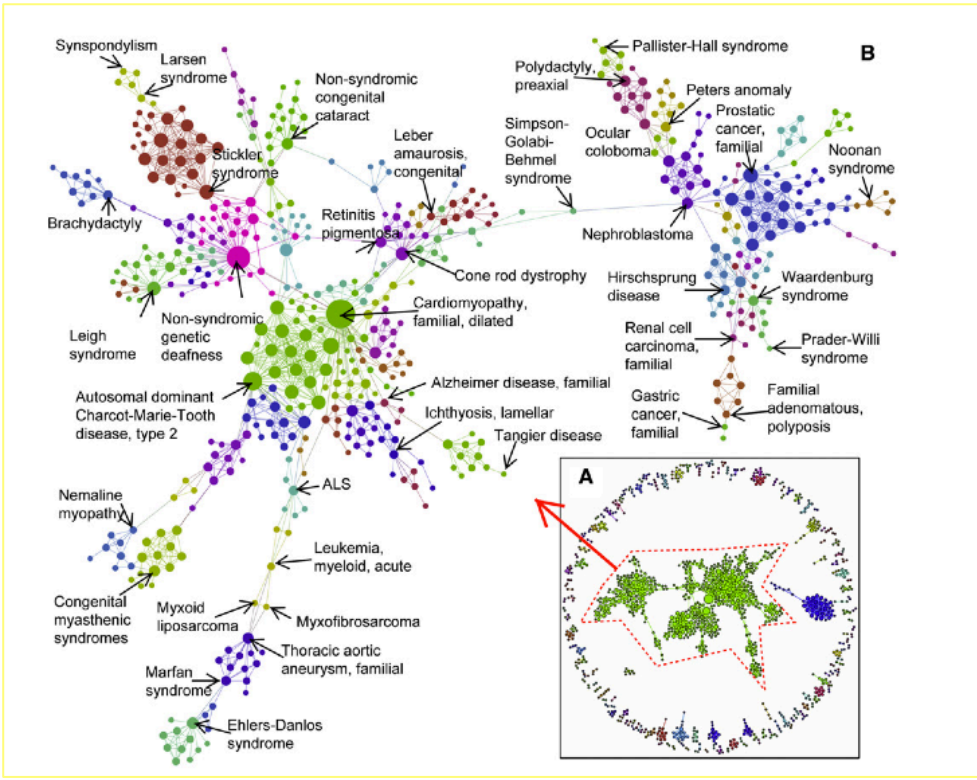
The Human Diseases Network

orphanet

The Orphan Disease Networks

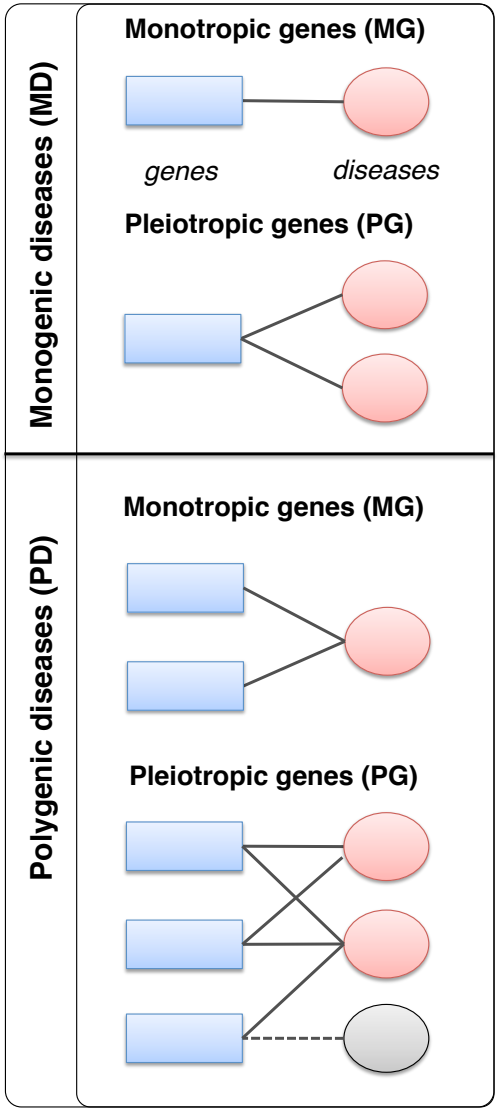


Goh et al. 2007



Zhang et al. 2011

Proposed classification (disease-gene)

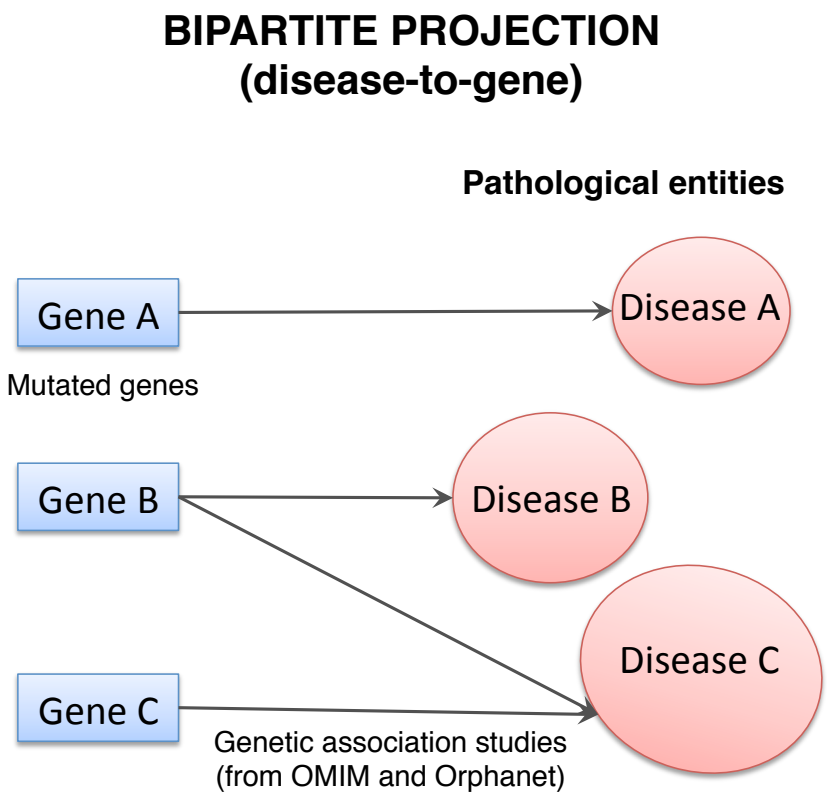


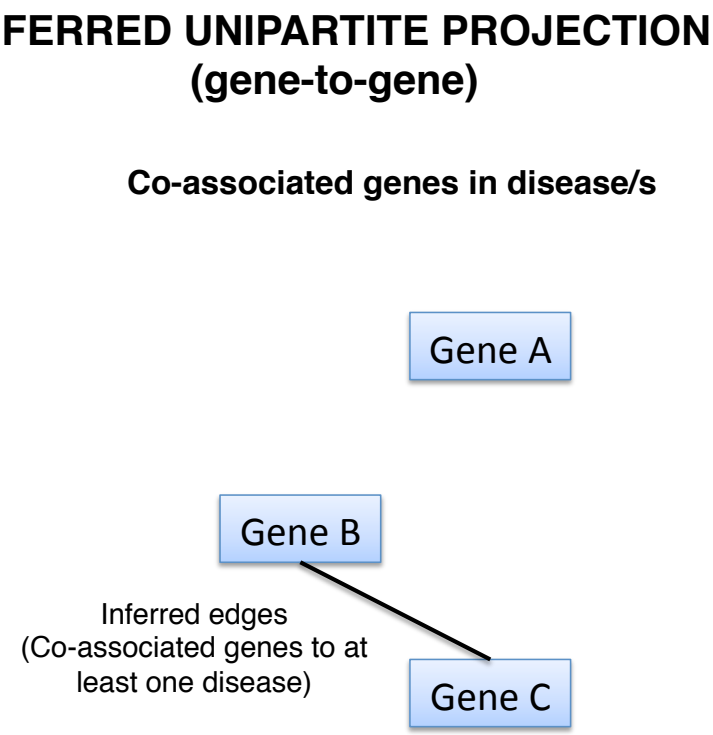
	Human Diseases Network		Orphan Disease Networks	
Subset	**Diseases per gene**	**Genes (%)**	**Diseases per gene**	**Genes (%)**
MD-MG	1.00	1431 (56.7)	1.00	717 (30.8)
MD-PG	2.57	639 (25.3)	2.71	435 (18.7)
PD-MG	0.46	379 (15.0)	0.40	908 (39.0)
PD-PG[a]	2.13	371 (14.7)	1.68	584 (25.1)
All genes[b]	1.24	2525 (100)	0.91	2331 (100)

[a]Pleiotropic genes associated with at least one polygenic diseases.
[b]All genes in HDN and ODN respectively.

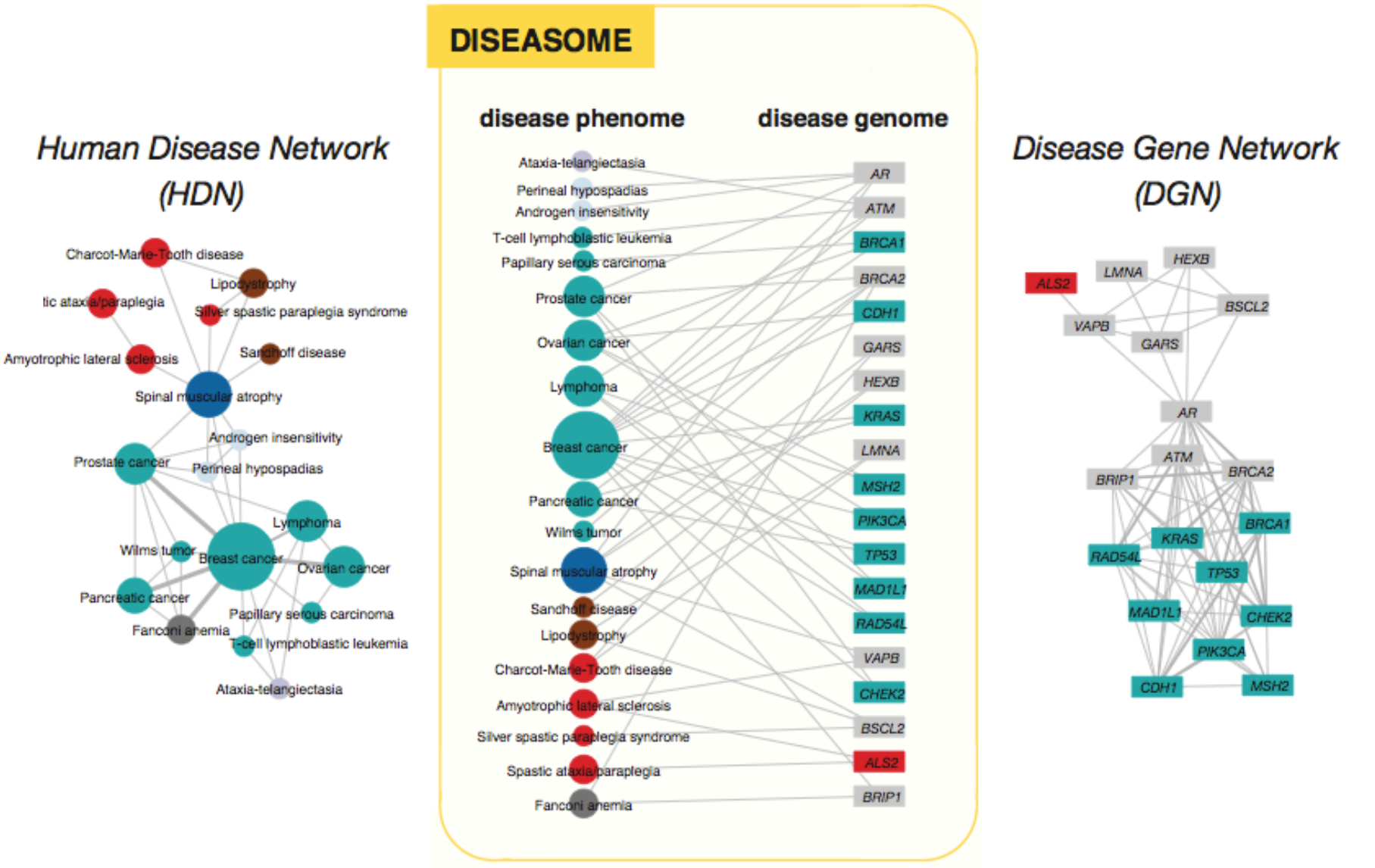
Strong differences between both inherited disease database

From KNOWN to INFERRED relationships



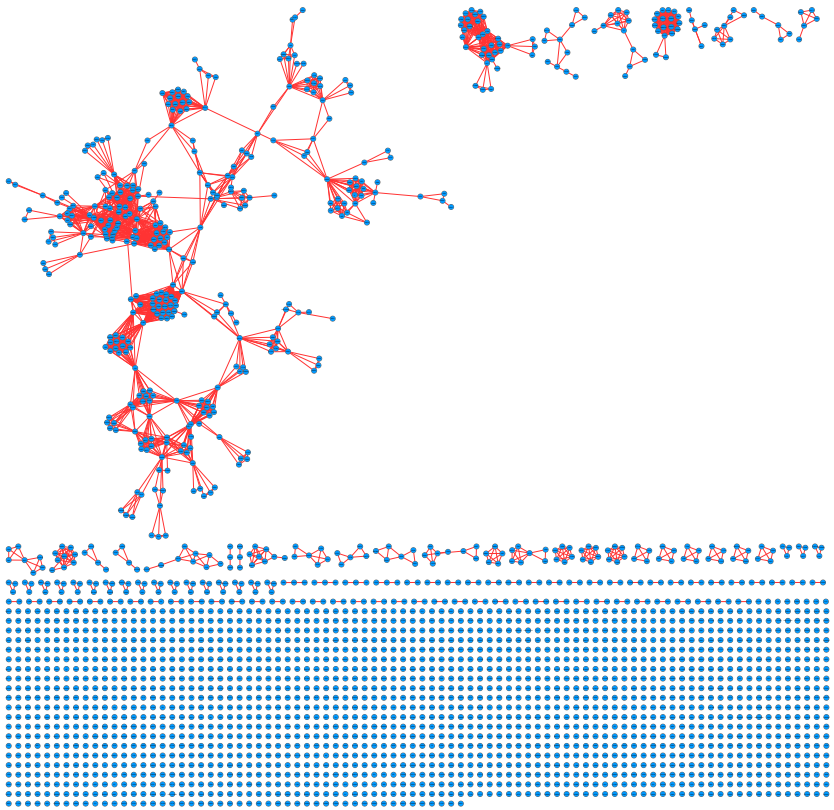


The Human Diseases Network

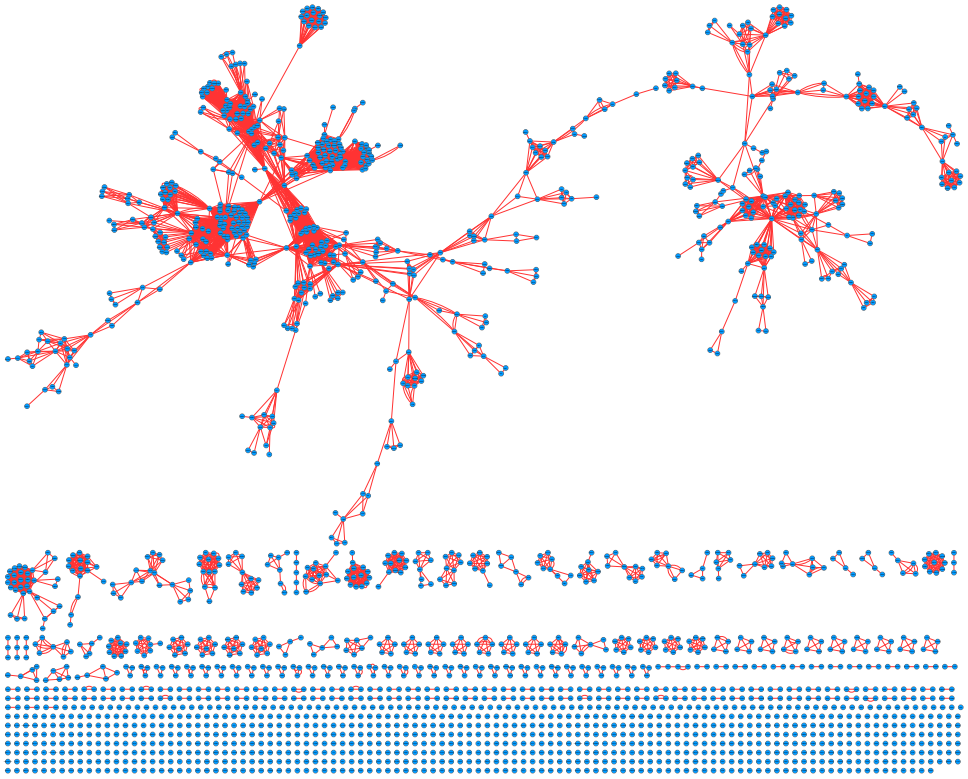


Inferred gene-gene (unipartite projections)

A) Human Diseases Gene Network
(gene-to-gene unipartite)
Connected nodes: 749
Unconnected nodes: 1776
Edges: 2654



B) Orphan Diseases Gene Network
(gene-to-gene unipartite)
Connected nodes: 1492
Unconnected nodes: 839
Edges: 6380



Network comparison HDGN vs ODGN

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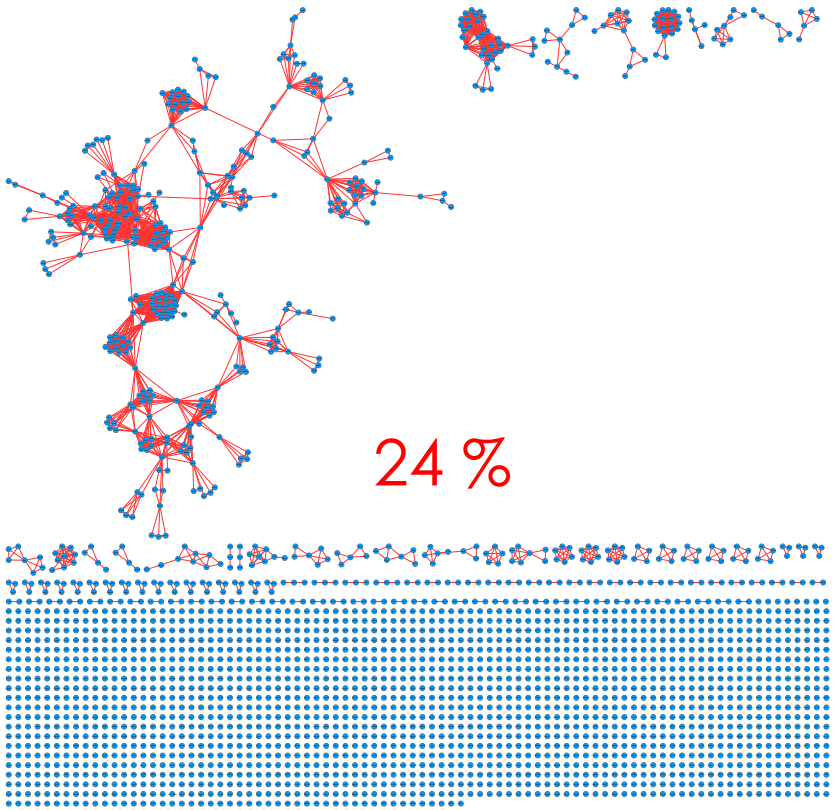

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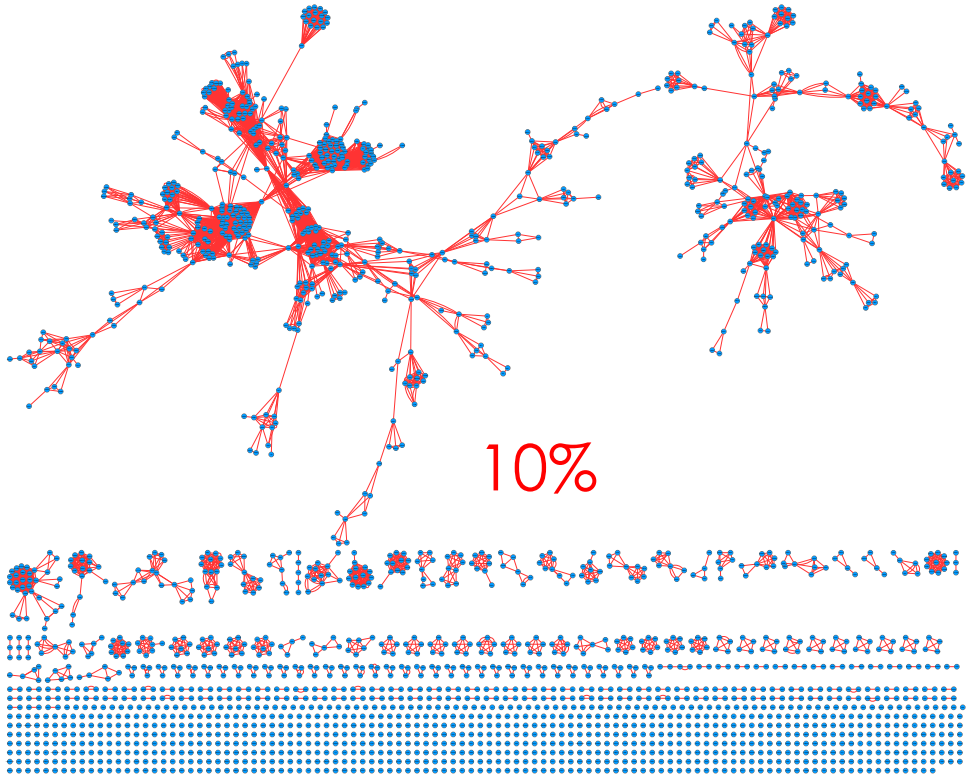
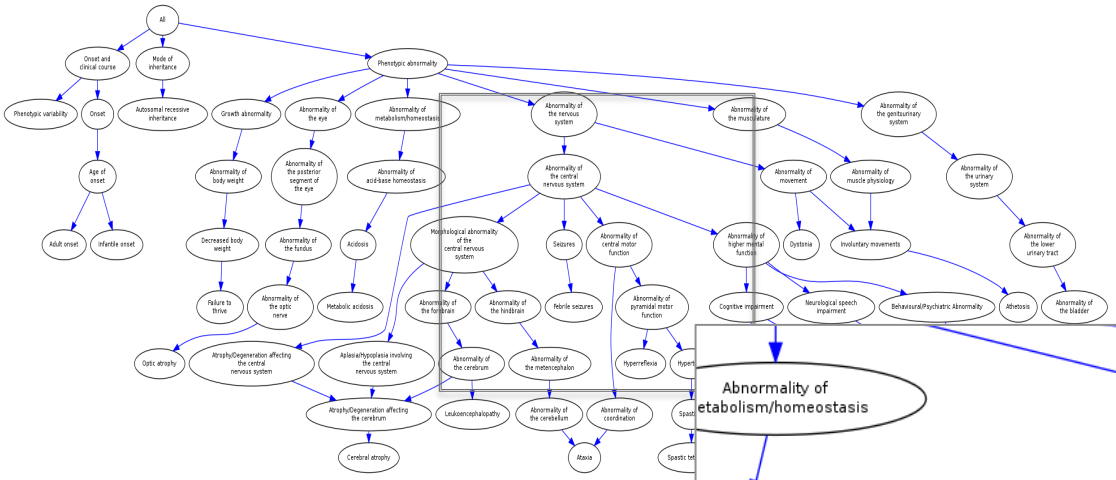
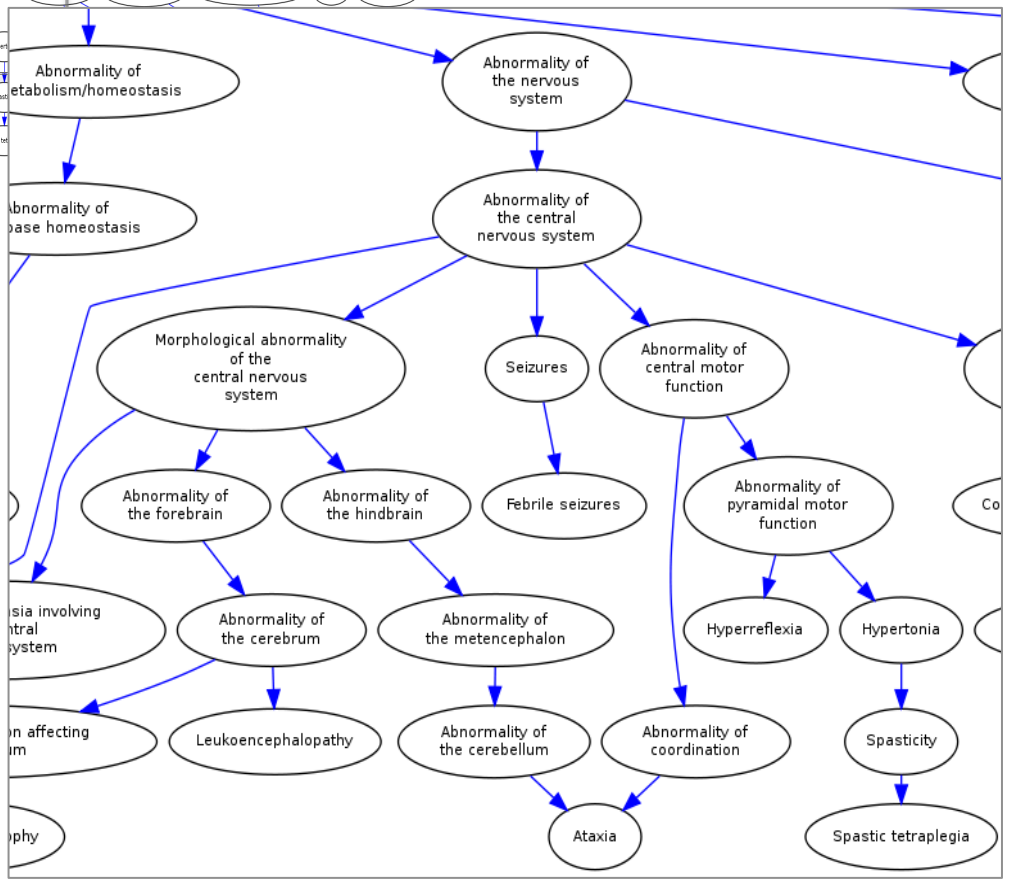


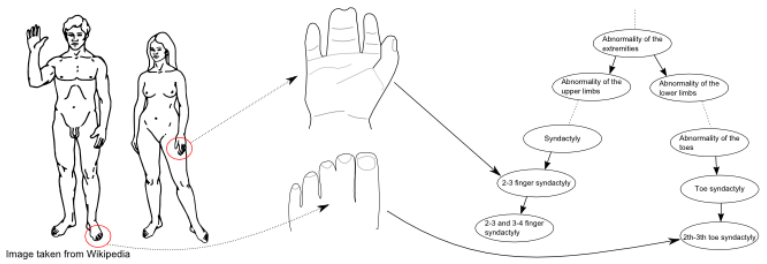
Understanding diseases as sets of phenotypes



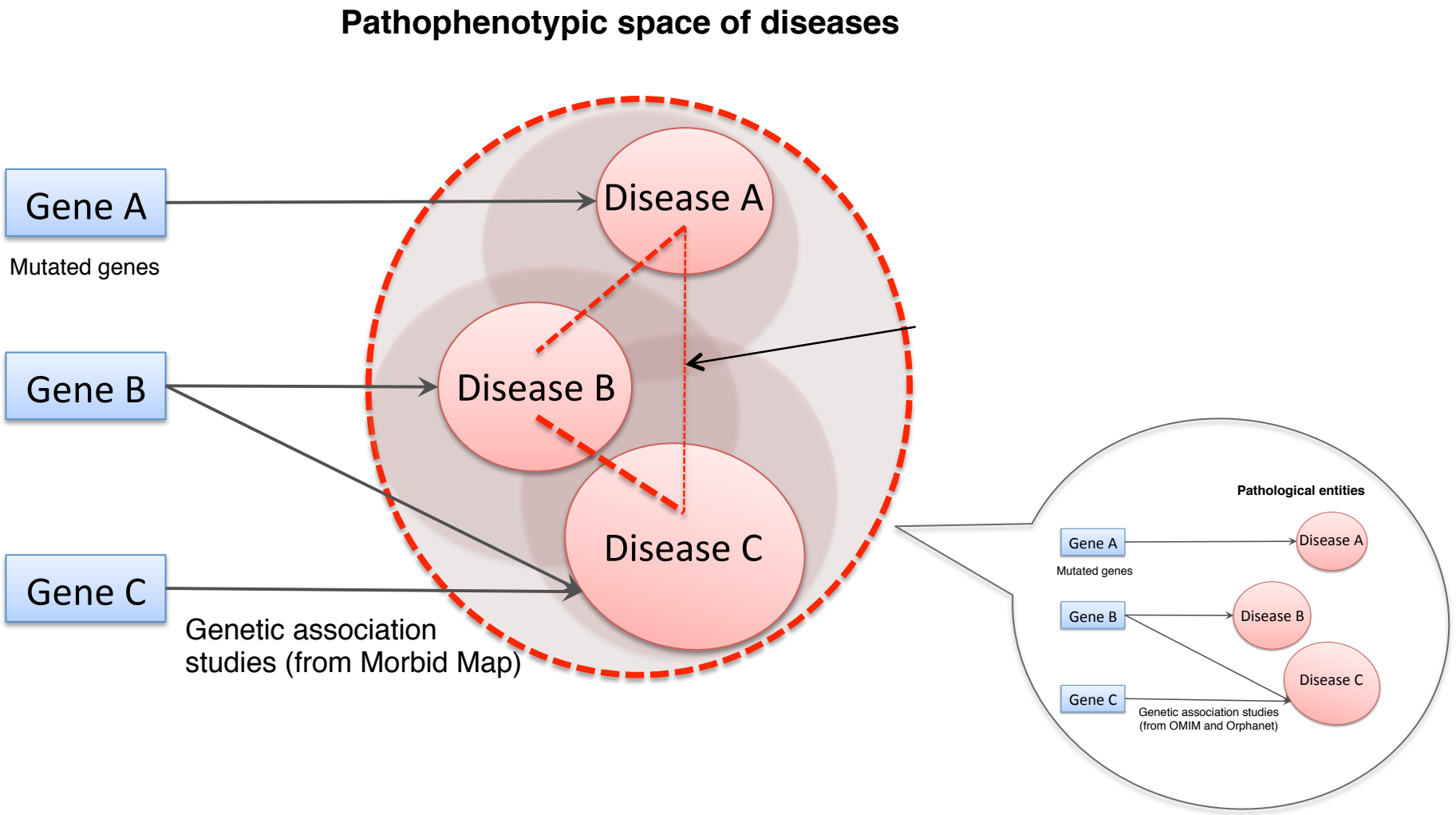


Human Phenotype Ontology

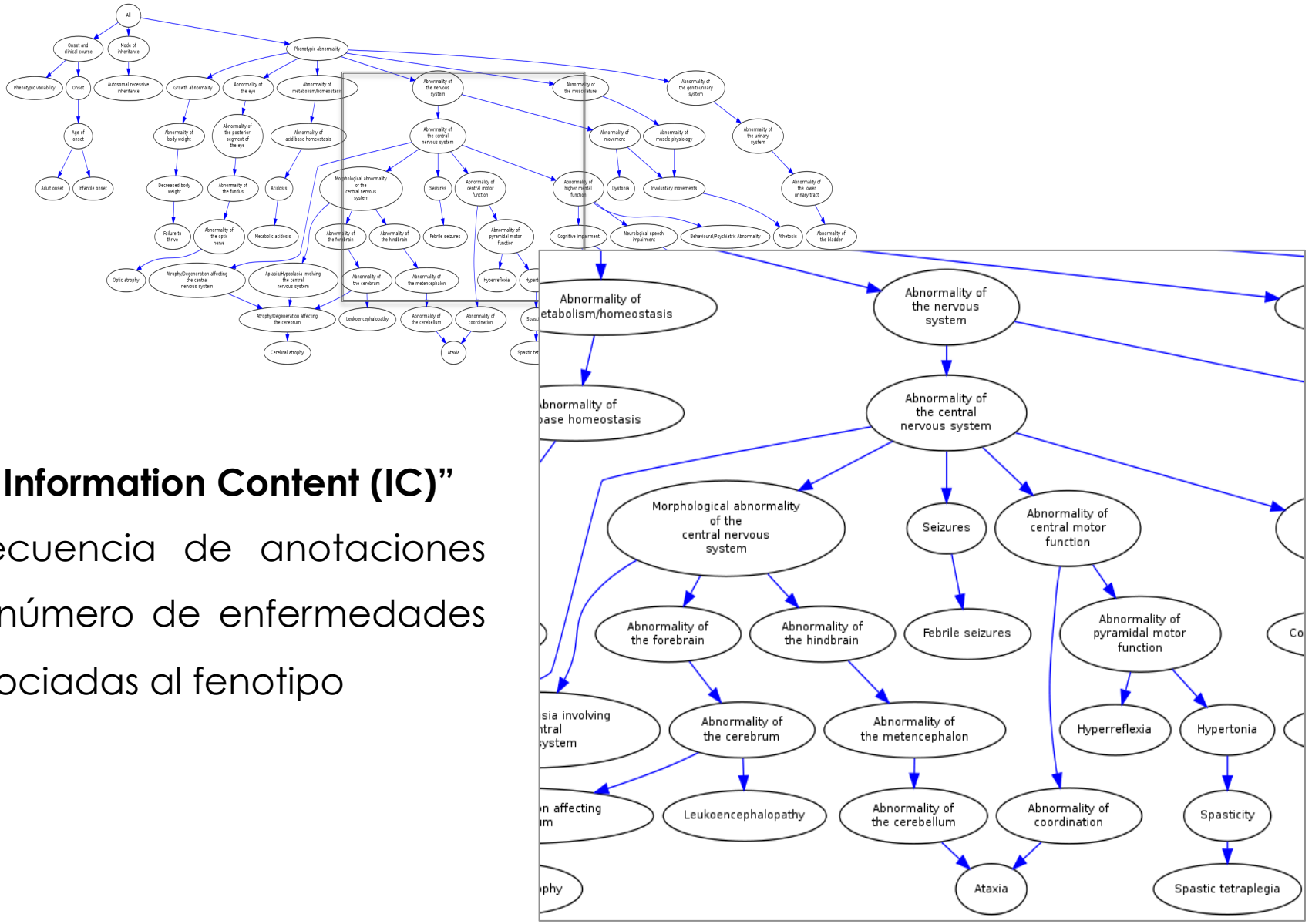
www.human-phenotype-ontology.org



Pathophenotypic space instead of diseases



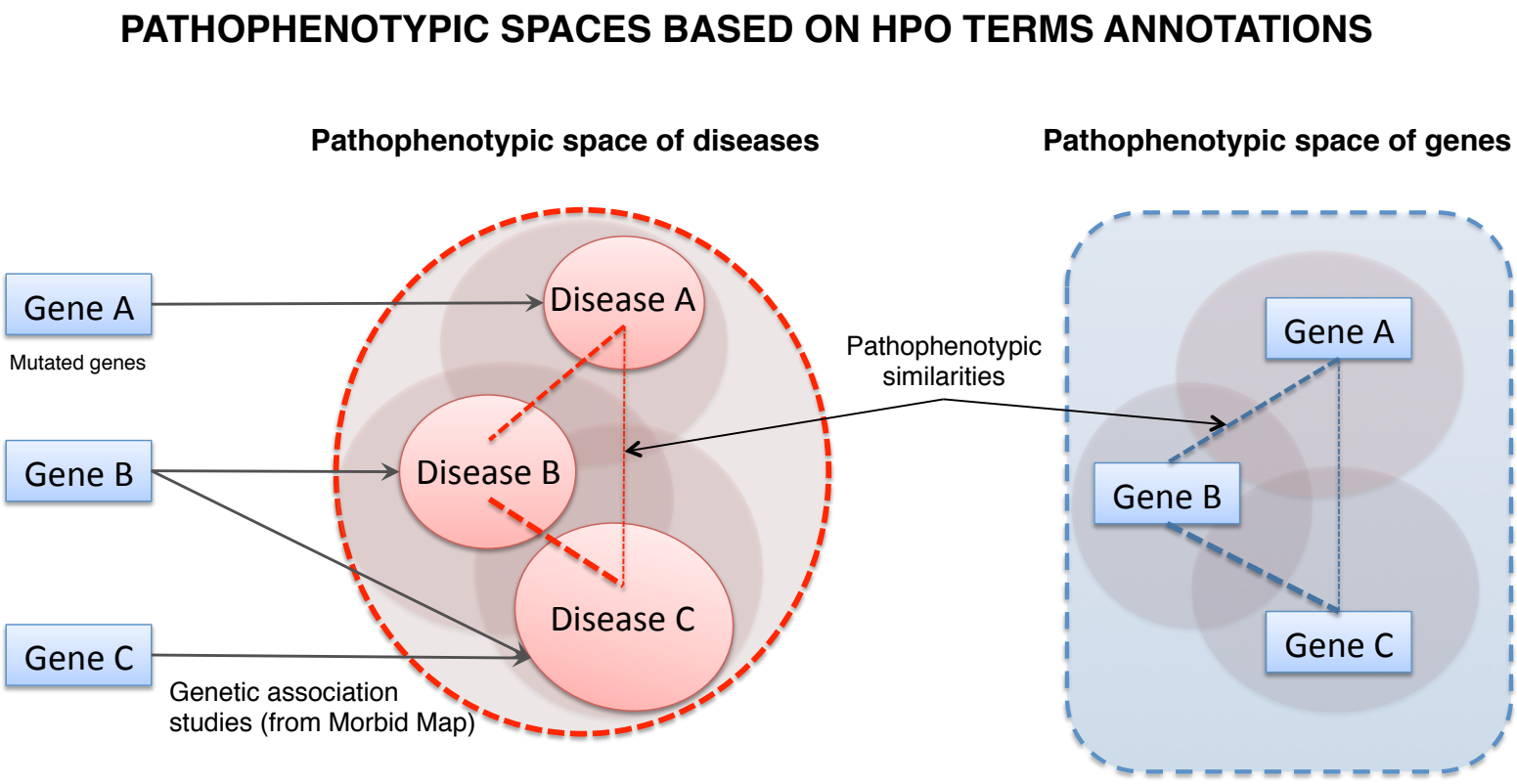
Understanding diseases as sets of phenotypes



“Information Content (IC)”

Frecuencia de anotaciones o número de enfermedades asociadas al fenotipo

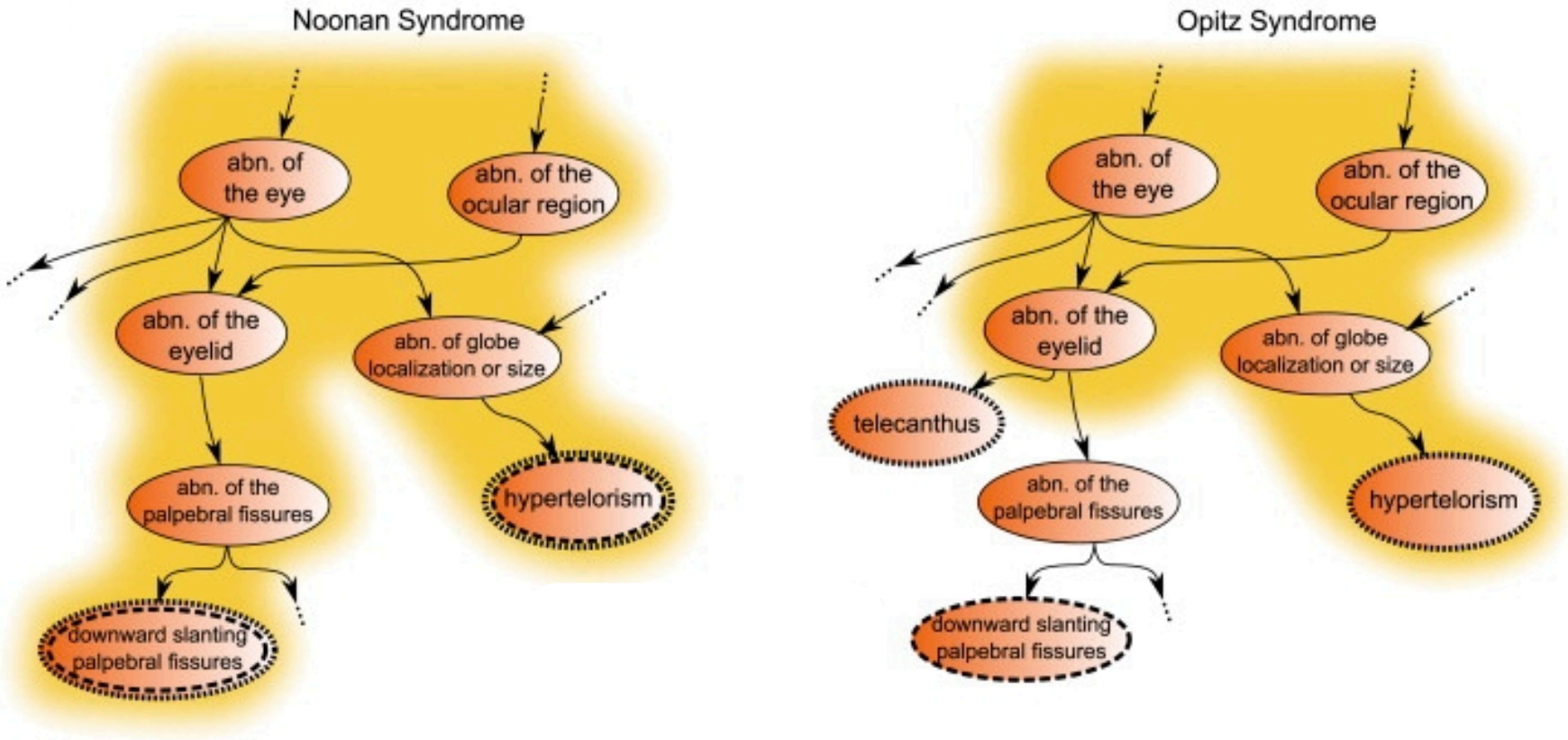
Pathophenotypic space for genes



Un fenotipo cambia su especificidad entre enfermedades y genes

"Information Content (IC)" de los fenotipos

Phenotypic similarity

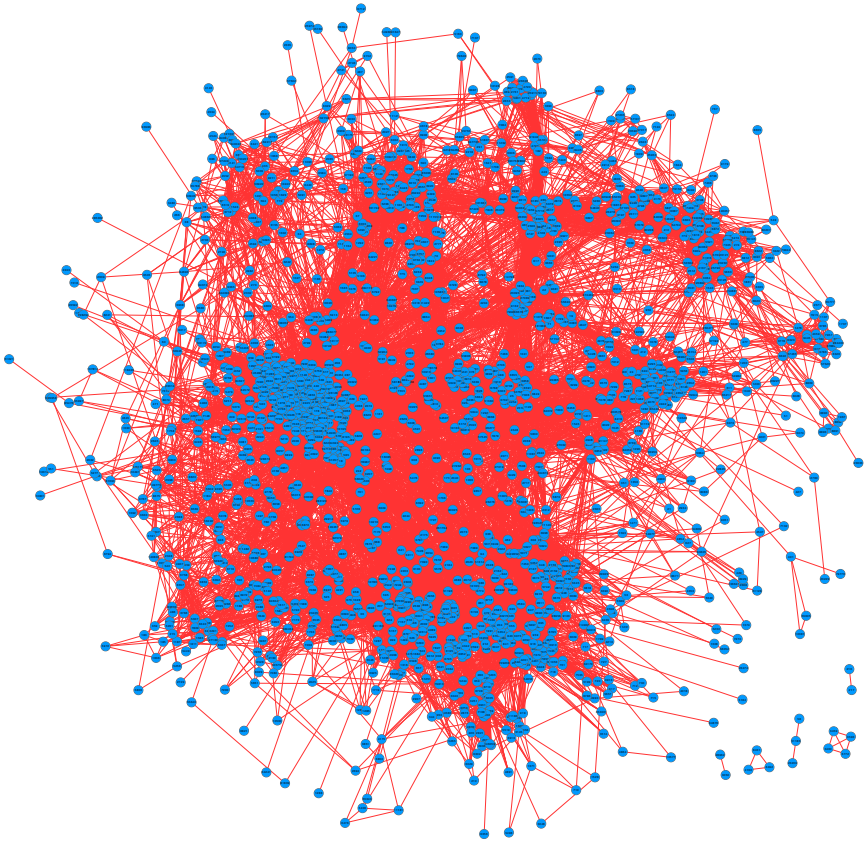


Renisk uses the most specific phenotypes

Robinson uses the media of all phenotypes

Human Pathophenotypic Similarity Gene Network (PSGN)

Connected nodes: 1705
Unconnected nodes: 0
Edges: 26197



Expanding phenotypic relationships to decrease the specificity

Network comparison HDGN, ODGN and PSGN

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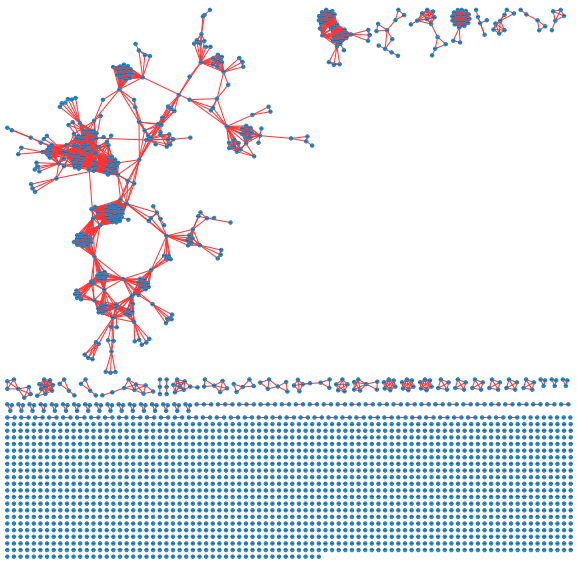

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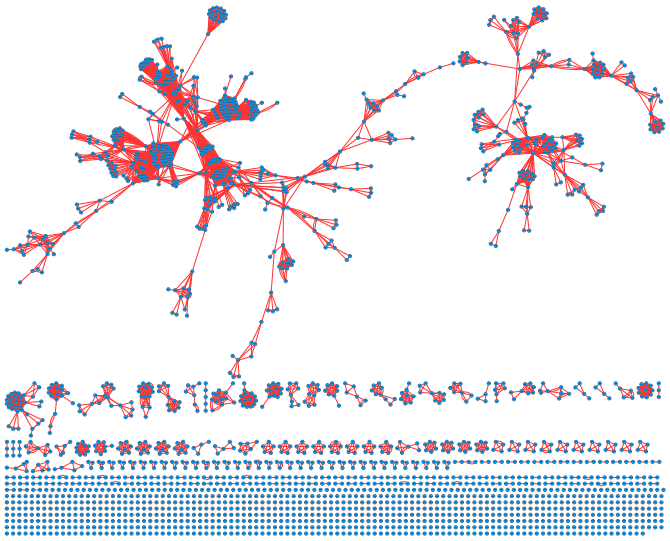
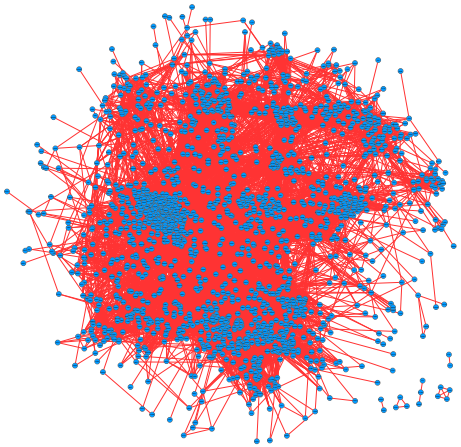
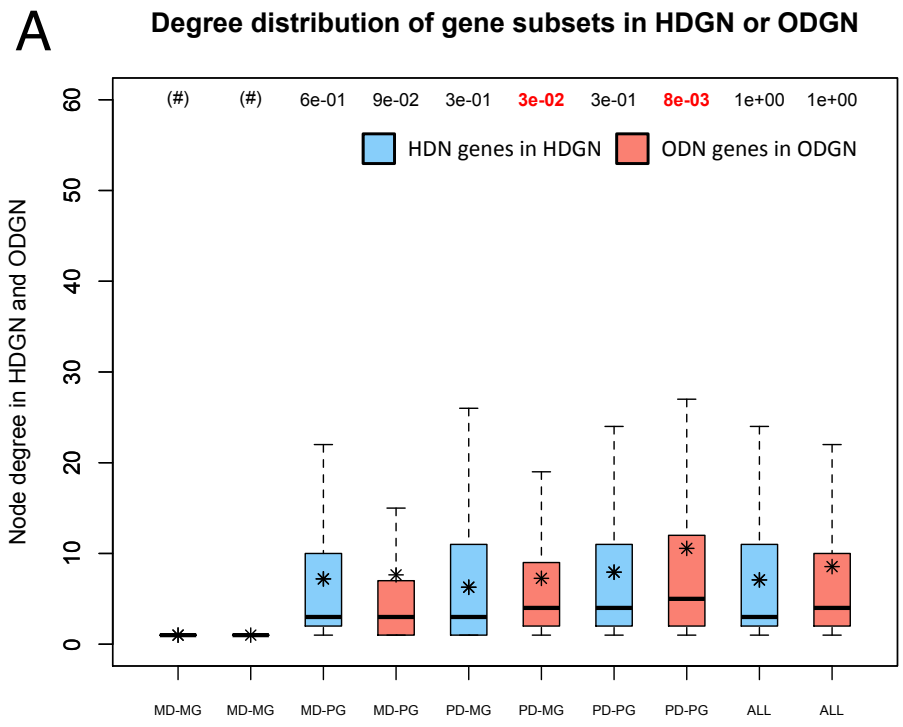
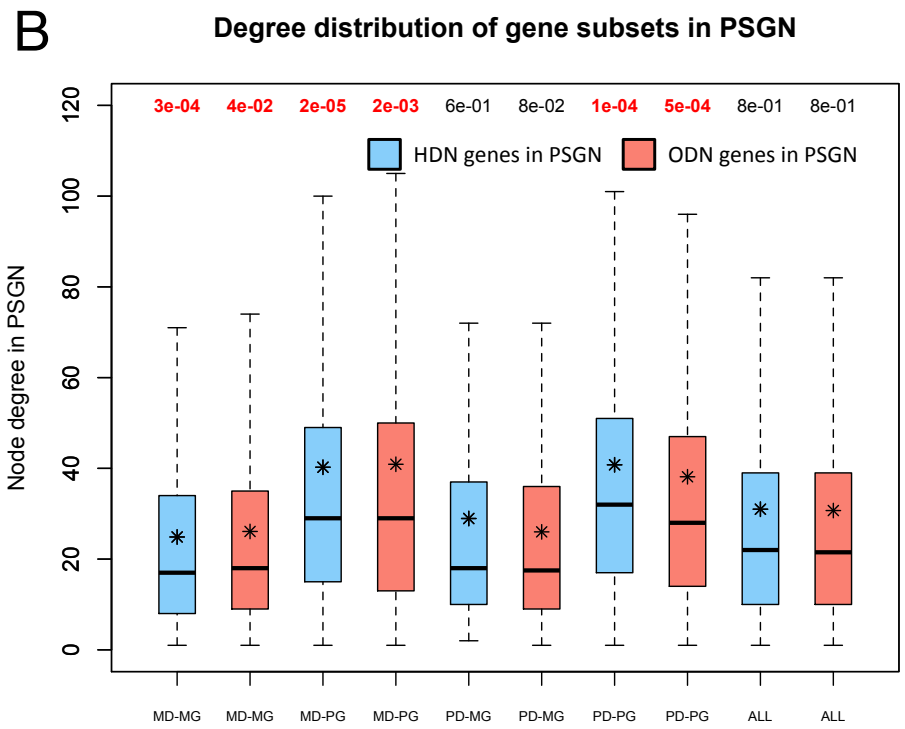


C) Pathophenotypic Similarity Gene Net
(gene-to-gene semantic similarity)
Connected nodes: 1705
Unconnected nodes: 0
Edges: 26197



Degree of genes in HDGN, ODGN and PSGN

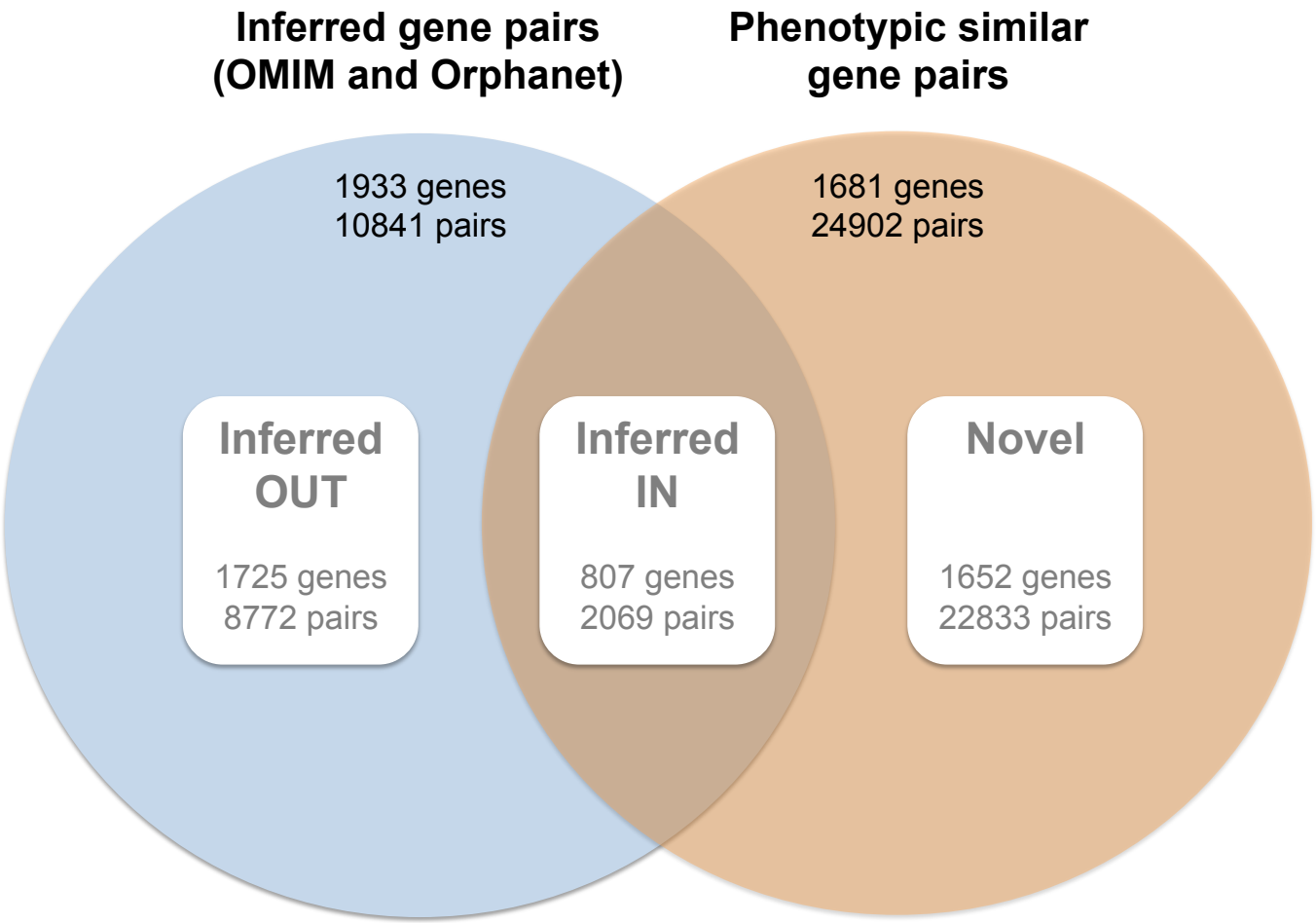




MD-MG 25 interacciones de media

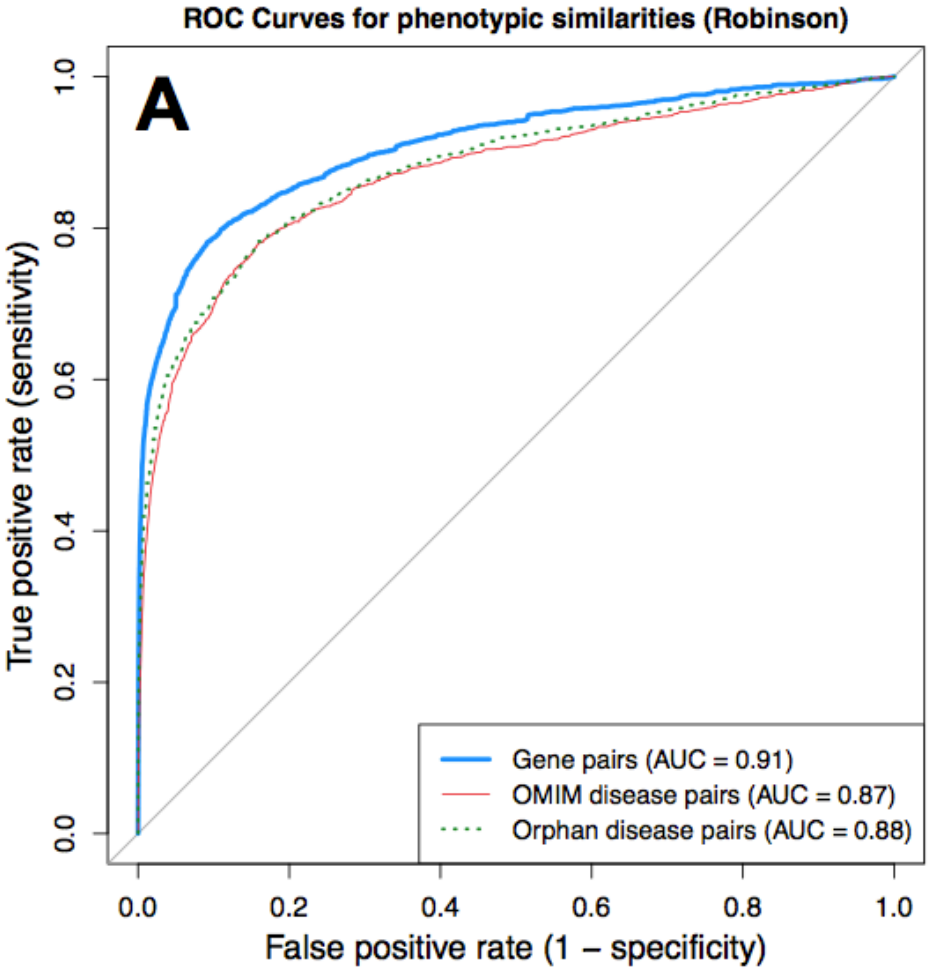
Más homogeneidad que HDN y ODGN

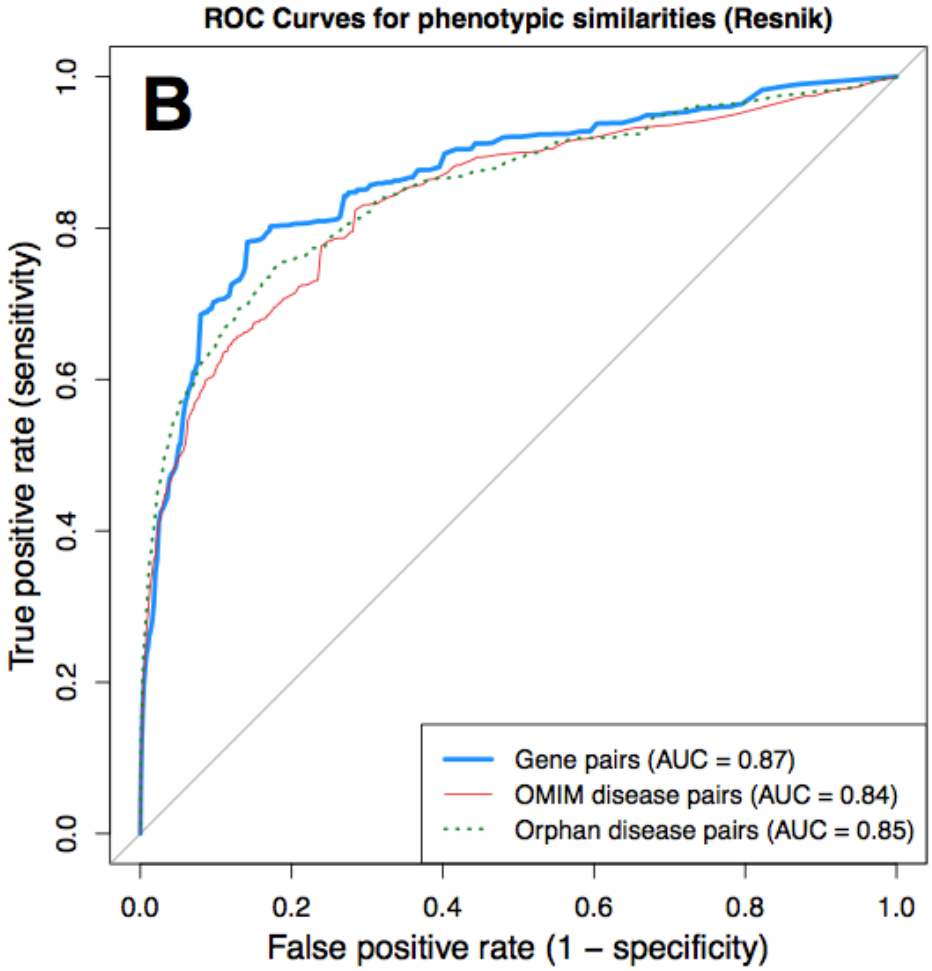
Venn diagram [(HDGN ∪ ODGN) ∩ PSGN]



Todos los genes anotados al menos 1 nueva relación

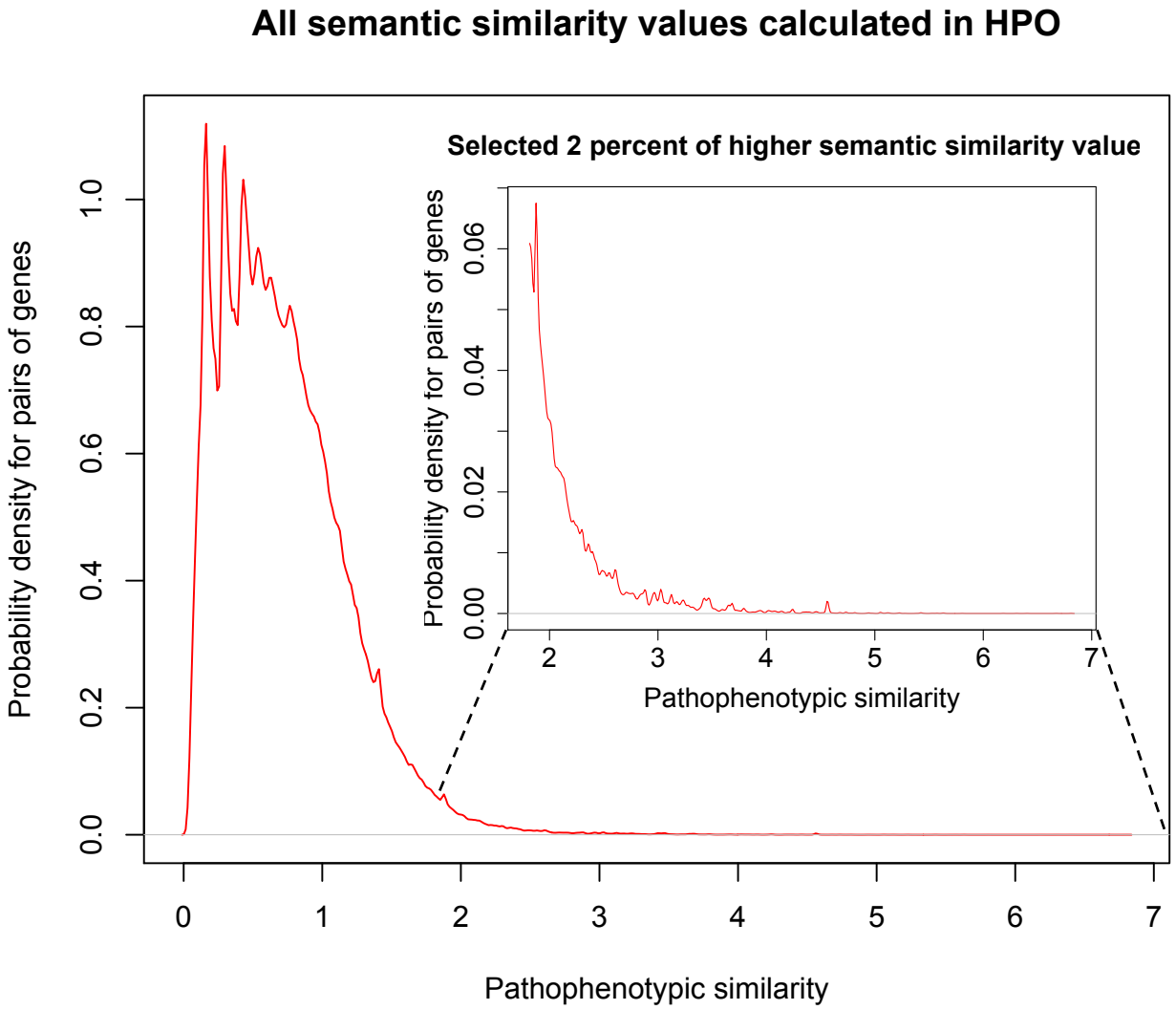
Performance validation (Phenotypic similarity vs. inference)





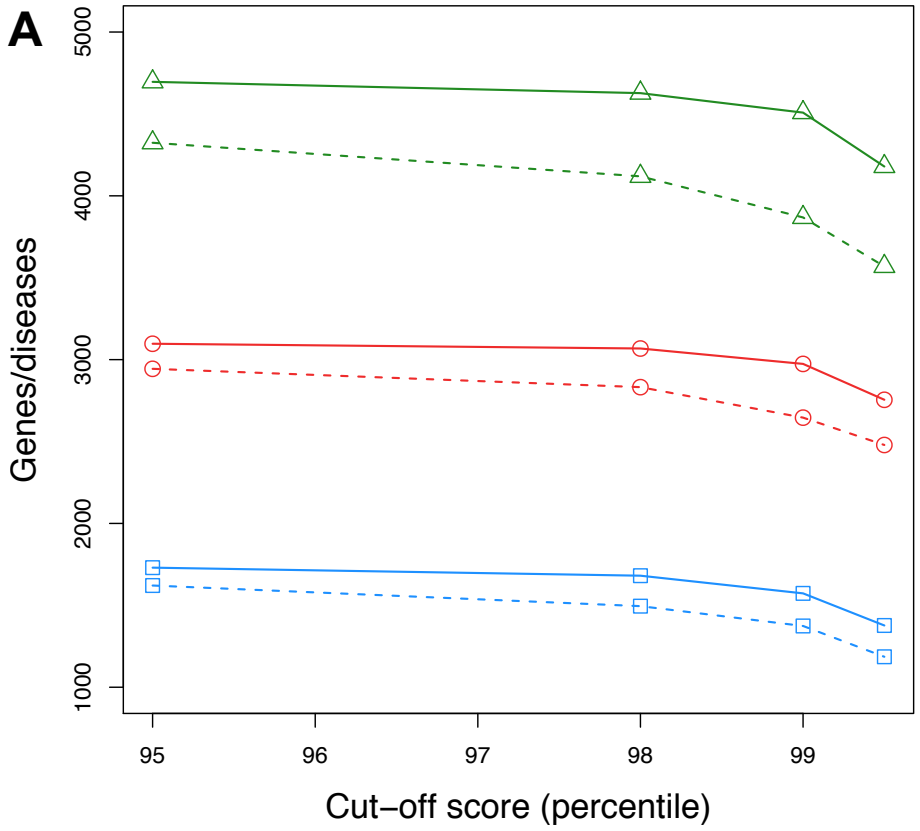
Robinson es una medida adecuada para la similitud fenotípica

Density function probability of phenotypic similarities



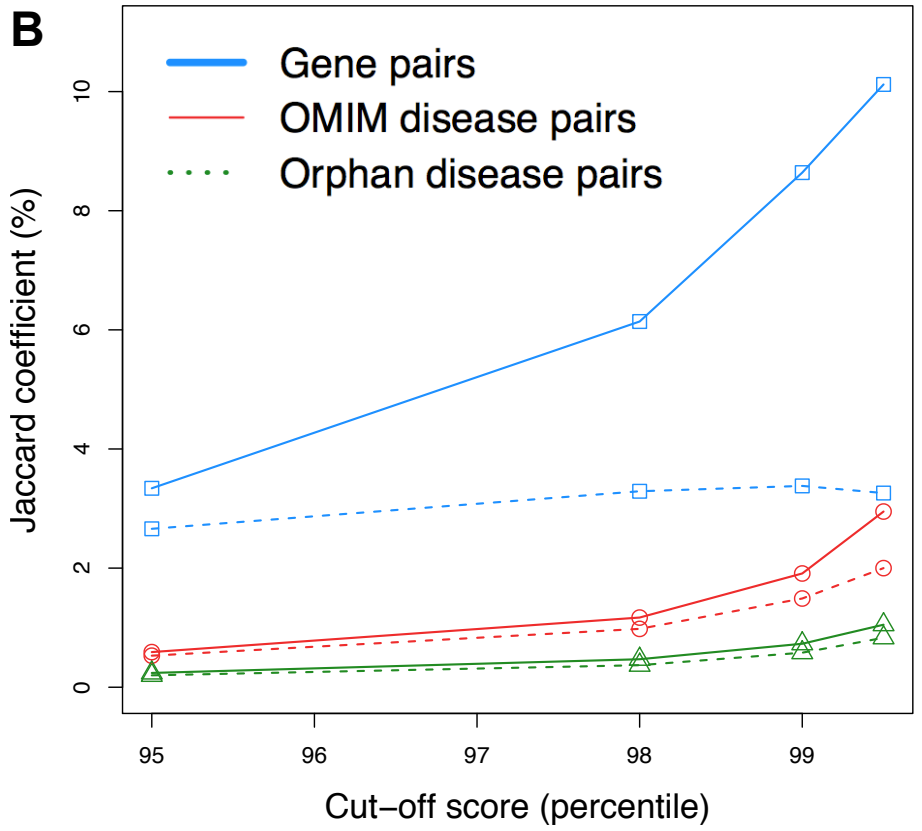
Robinson es una medida adecuada para la similitud fenotípica

Optimal Statistical Cut-Off (pragmatic)



From 98th we loss information

TOMORROW

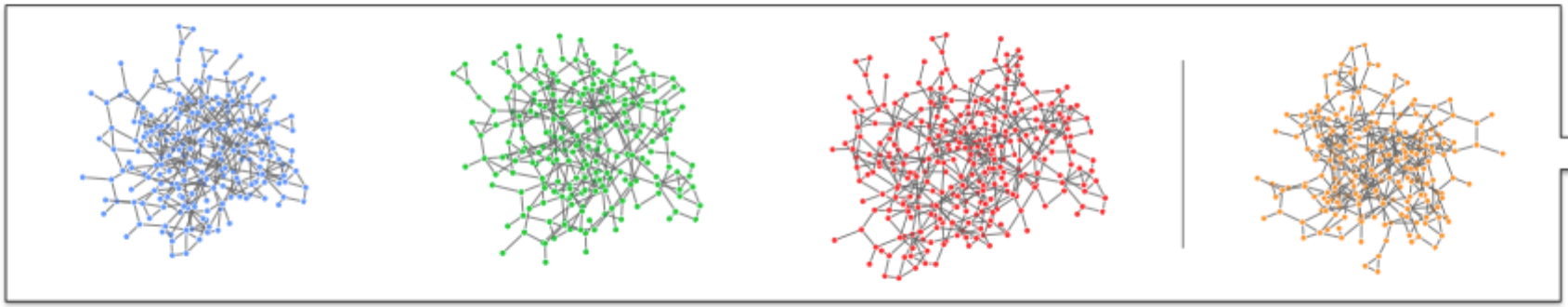


From 98th we increase similarity with inferred

1. CONSTRUCTION OF INTERACTOMES AND SEMANTIC SIMILARITY BASED NETWORKS

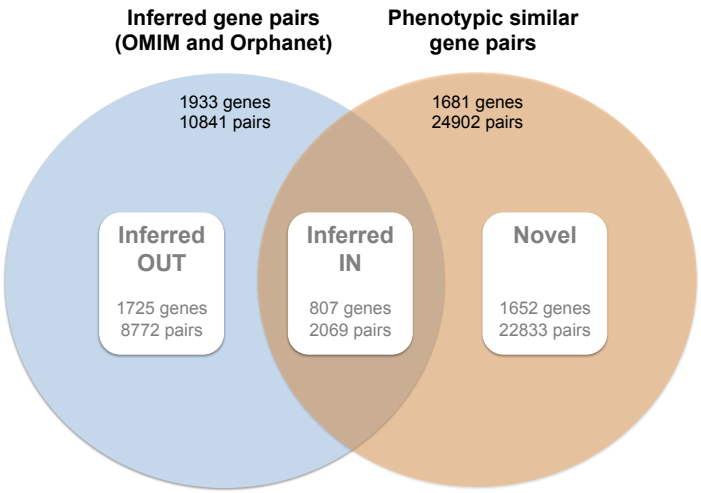
GO BP ontology | **GO gene annotations** | **HPO ontology** | **HPO gene annotations**

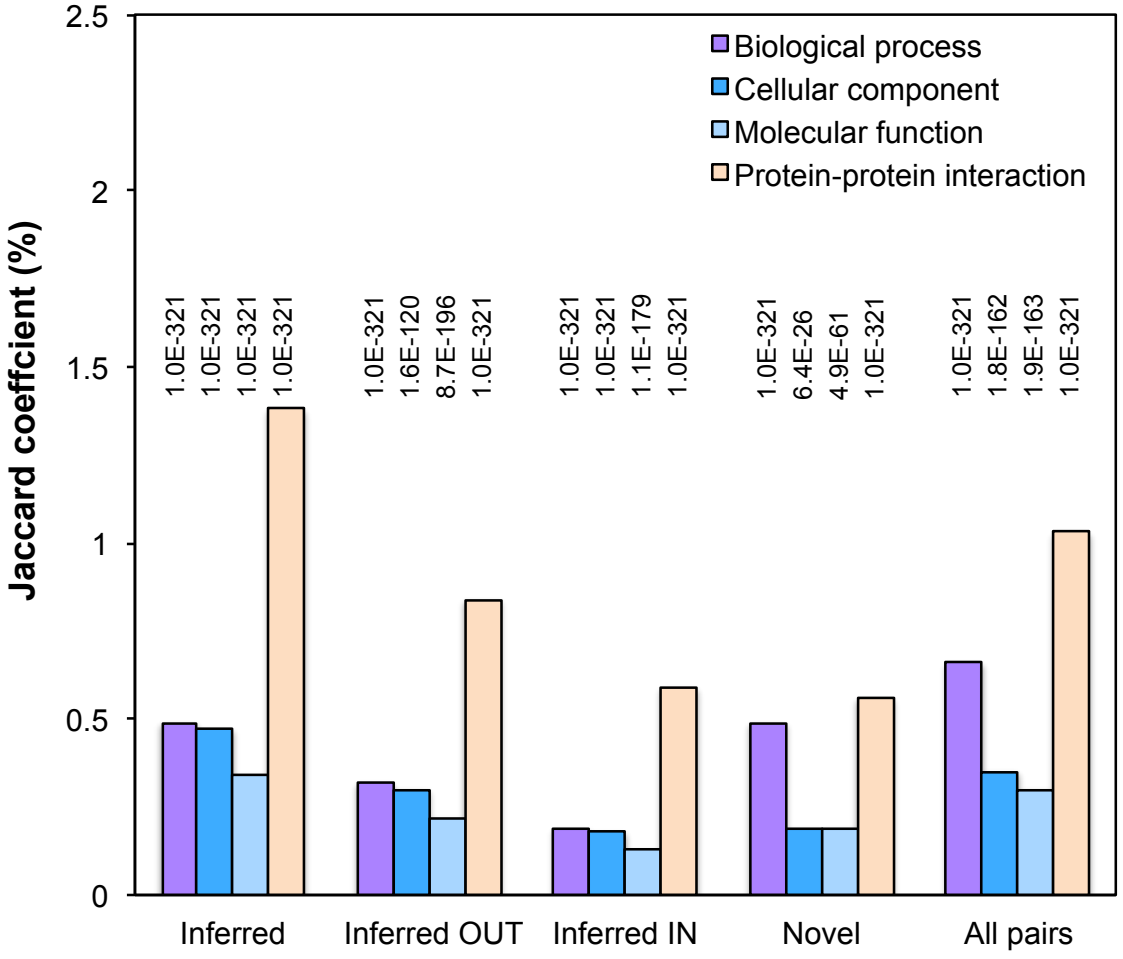
CRG Human Interactome (Bossi et al. 2009)	Flux Balance Analysis of Human Metabolic Network Recon 1 (Veeramani et al. 2009)	Semantic similarity measure (Resnik et al. 1995)	Semantic similarity measure (Köhler et al. 2009)
At least one experimental evidence	*Filtering out "metscore" gene pairs equal to zero*	**Functional similarity scores between genes**	**Pathophenotypic similarity scores between genes**
Mapping ENSEMBL Gene ID to Entrez GeneID	*Filtering out low flux correlation gene pairs (equal or under 0.1)*	*Filtering out low score gene pairs (under 99.5th percentile)*	*Filtering out low score gene pairs (under 98th percentile)*
PIN 9580 nodes 74657 edges	**MGN** 535 nodes 9812 edges	**FSGN** 9157 nodes 496973 edges	**PSGN** 1705 nodes 26197 edges



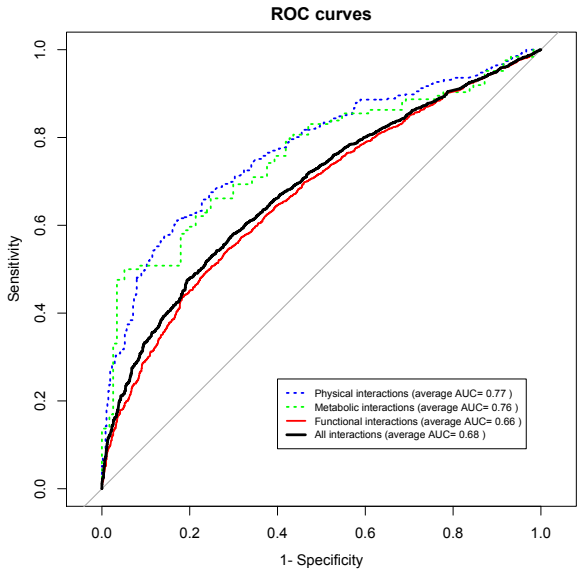
BIOMOLECULAR INTERACTOMES **PSGN**

Network Comparisons Between Interactomes and PSGN Subsets

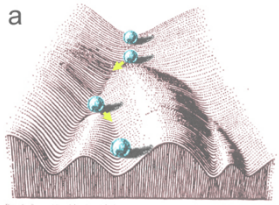




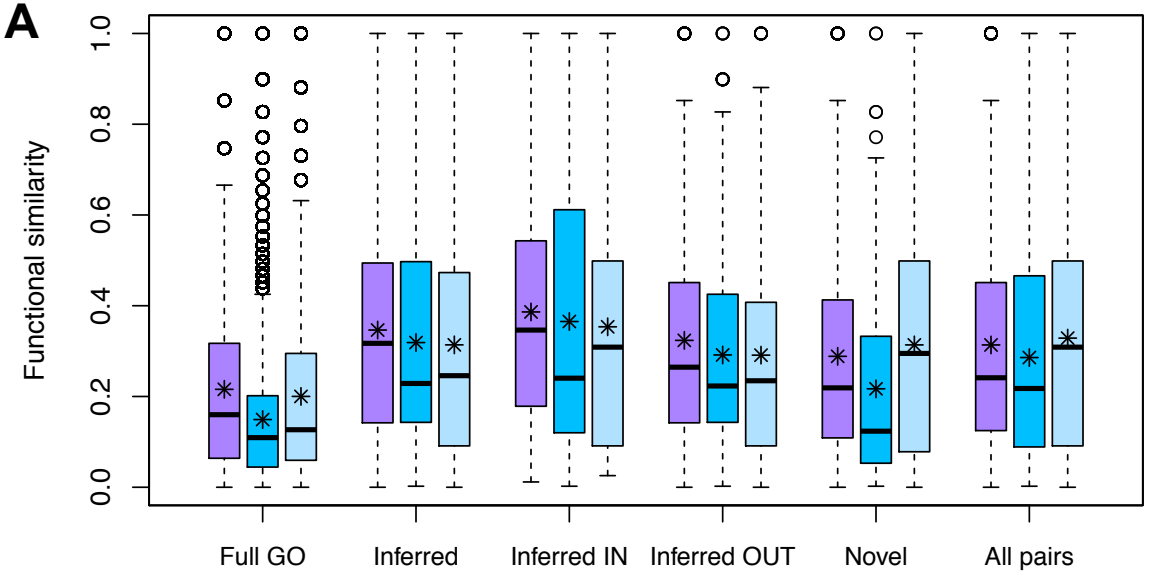
Intersection between Phenotypic and Functional interactions has higher similarity scores



Natural (biological) networks evolved to be robust to genetic, environmental and stochastic perturbations. GOOD level of abstraction, less precision



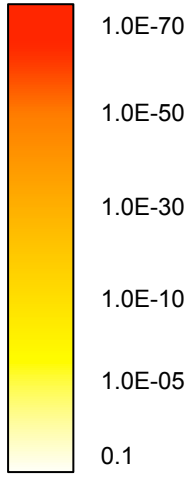
A



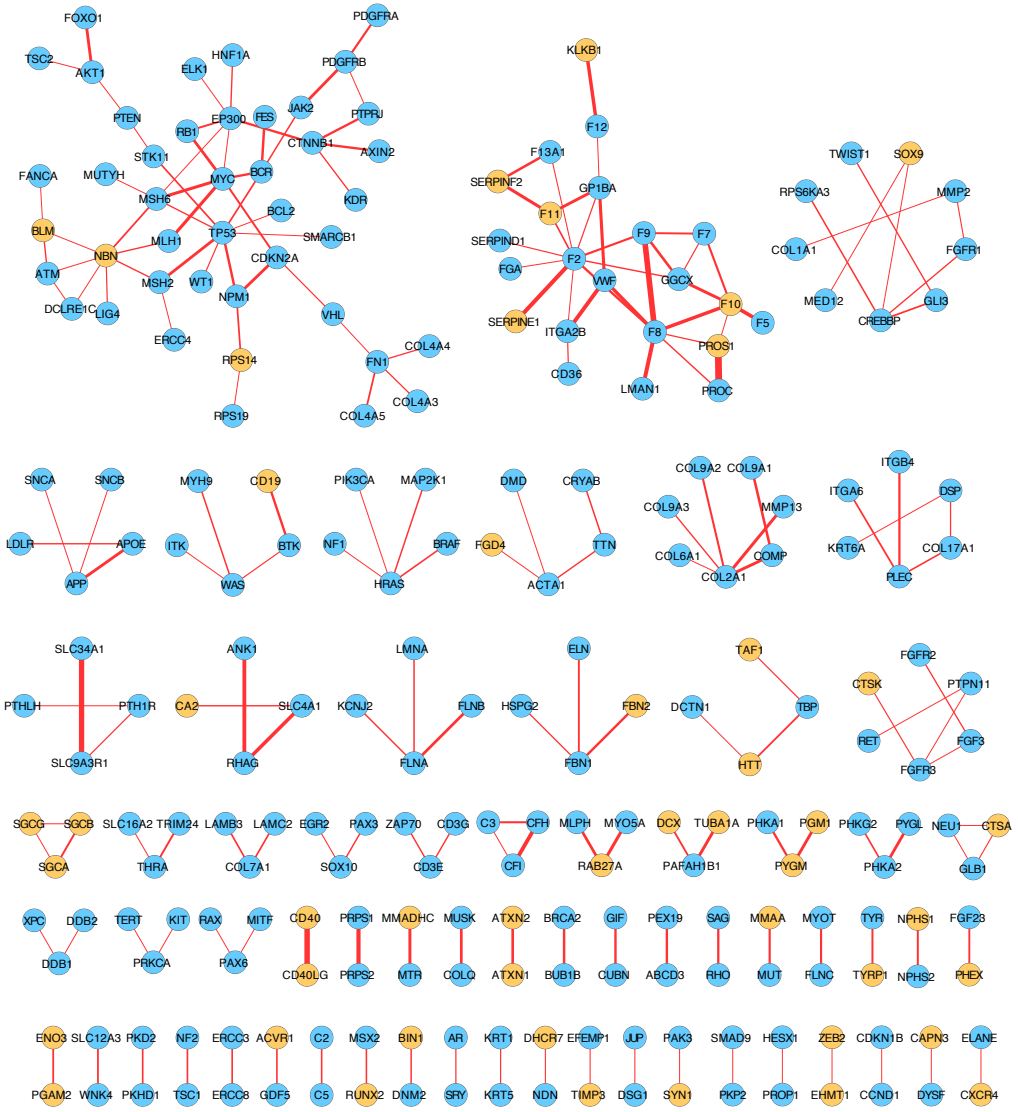
B

Heat map of Mann-Whitney P-values from the distribution comparisons

	Biological process	Cellular component	Molecular function
Inferred	3.53E-30	8.23E-69	3.00E-11
Inferred IN	5.19E-19	2.78E-32	2.32E-06
Inferred OUT	6.00E-13	6.38E-38	3.81E-06
Novel	4.46E-10	1.91E-04	1.37E-06
All pairs	1.87E-22	5.49E-27	1.56E-11

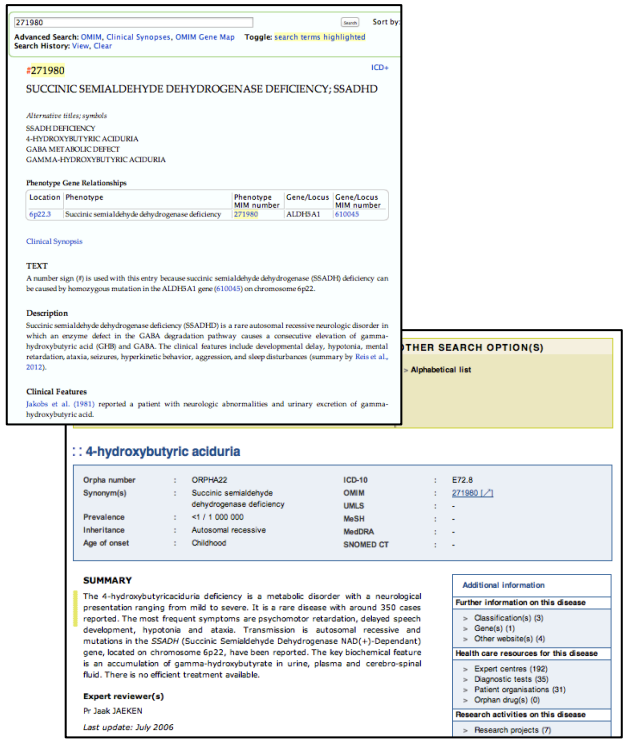


Novel phenotypic similarities ∩ protein interactions



Conclusion I

Migración de bases de datos descriptivas a gestionar esa información en red. **Network Medicine**


271980

Advanced Search: OMIM, Clinical Synopses, OMIM Gene Map Toggle: search terms highlighted
Search History: View, Clear

#271980

SUCCINIC SEMIALDEHYDE DEHYDROGENASE DEFICIENCY; SSADHD

Alternative titles; symbols
SSADH DEFICIENCY
4-HYDROXYBUTYRIC ACIDURIA
GABA METABOLIC DEFECT
GAMMA-HYDROXYBUTYRIC ACIDURIA

Phenotype Gene Relationships

Location	Phenotype	Phenotype MIM number	Gene/Locus	Gene/Locus MIM number
6p22.3	Succinic semialdehyde dehydrogenase deficiency	271980	ALDH5A1	610045

Clinical Synopsis

TEXT
A number sign (#) is used with this entry because succinic semialdehyde dehydrogenase (SSADH) deficiency can be caused by homozygous mutation in the ALDH5A1 gene (610045) on chromosome 6p22.

Description
Succinic semialdehyde dehydrogenase deficiency (SSADHD) is a rare autosomal recessive neurologic disorder in which an enzyme defect in the GABA degradation pathway causes a consecutive elevation of gamma-hydroxybutyric acid (GHB) and GABA. The clinical features include developmental delay, hypotonia, mental retardation, ataxia, seizures, hyperkinetic behavior, aggression, and sleep disturbances (summary by Reis et al., 2012).

Clinical Features
Jakobs et al. (1981) reported a patient with neurologic abnormalities and urinary excretion of gamma-hydroxybutyric acid.

OTHER SEARCH OPTION(S)
Alphabetical list

: : 4-hydroxybutyric aciduria

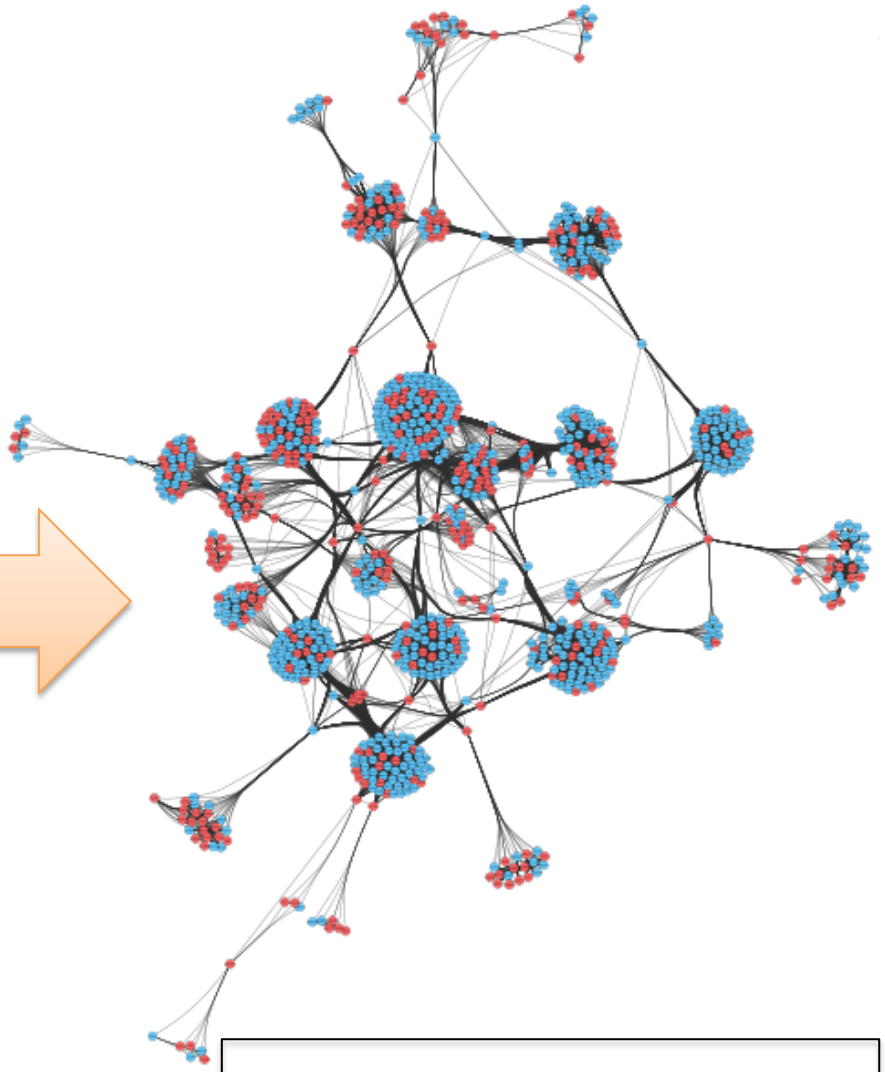
Orpha number	:	ORPHA22	ICD-10	:	E72.8
Synonym(s)	:	Succinic semialdehyde dehydrogenase deficiency	OMIM	:	271980 [ ]
			UMLS	:	-
Prevalence	:	<1 / 1 000 000	MeSH	:	-
Inheritance	:	Autosomal recessive	MedDRA	:	-
Age of onset	:	Childhood	SNOMED CT	:	-

SUMMARY
The 4-hydroxybutyricaciduria deficiency is a metabolic disorder with a neurological presentation ranging from mild to severe. It is a rare disease with around 350 cases reported. The most frequent symptoms are psychomotor retardation, delayed speech development, hypotonia and ataxia. Transmission is autosomal recessive and mutations in the *SSADH* (Succinic Semialdehyde Dehydrogenase NAD(+)-Dependant) gene, located on chromosome 6p22, have been reported. The key biochemical feature is an accumulation of gamma-hydroxybutyrate in urine, plasma and cerebro-spinal fluid. There is no efficient treatment available.

Expert reviewer(s)
Pr Jaak JAEKEN

Last update: July 2006

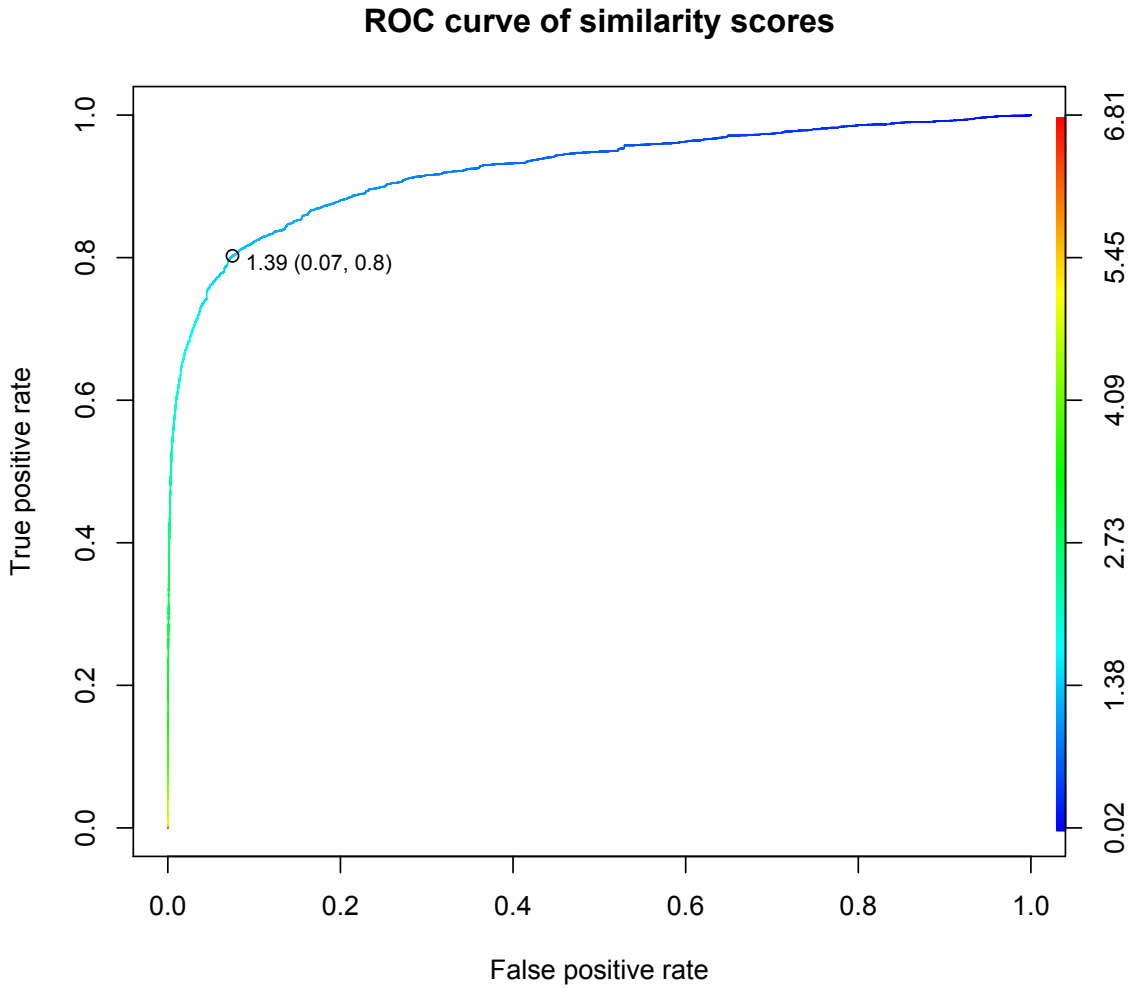
Additional information
Further information on this disease
> Classification(s) (3)
> Gene(s) (1)
> Other website(s) (4)
Health care resources for this disease
> Expert centres (192)
> Diagnostic tests (35)
> Patient organisations (31)
> Orphan drug(s) (0)
Research activities on this disease
> Research projects (7)



ENCODE

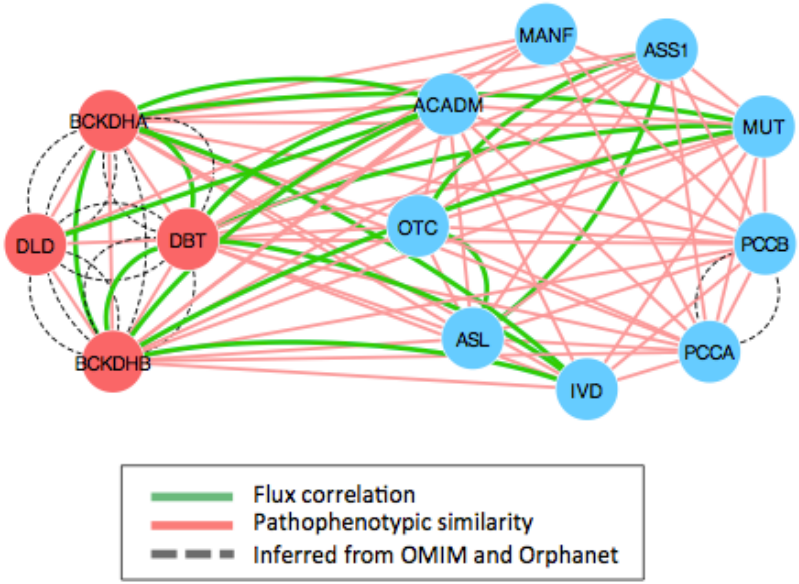
Fenotipos intermedios o moleculares

Conclusion II

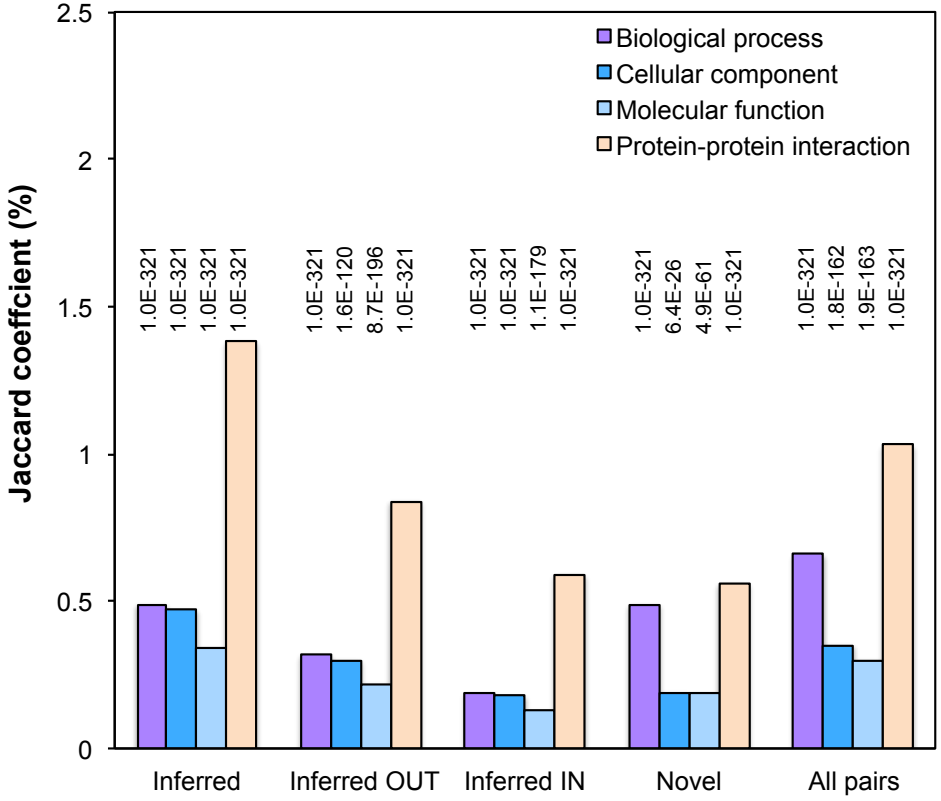


Similitud semántica es un modelo pragmático para estudiar las relaciones fenotípicas y funcionales

Conclusion III



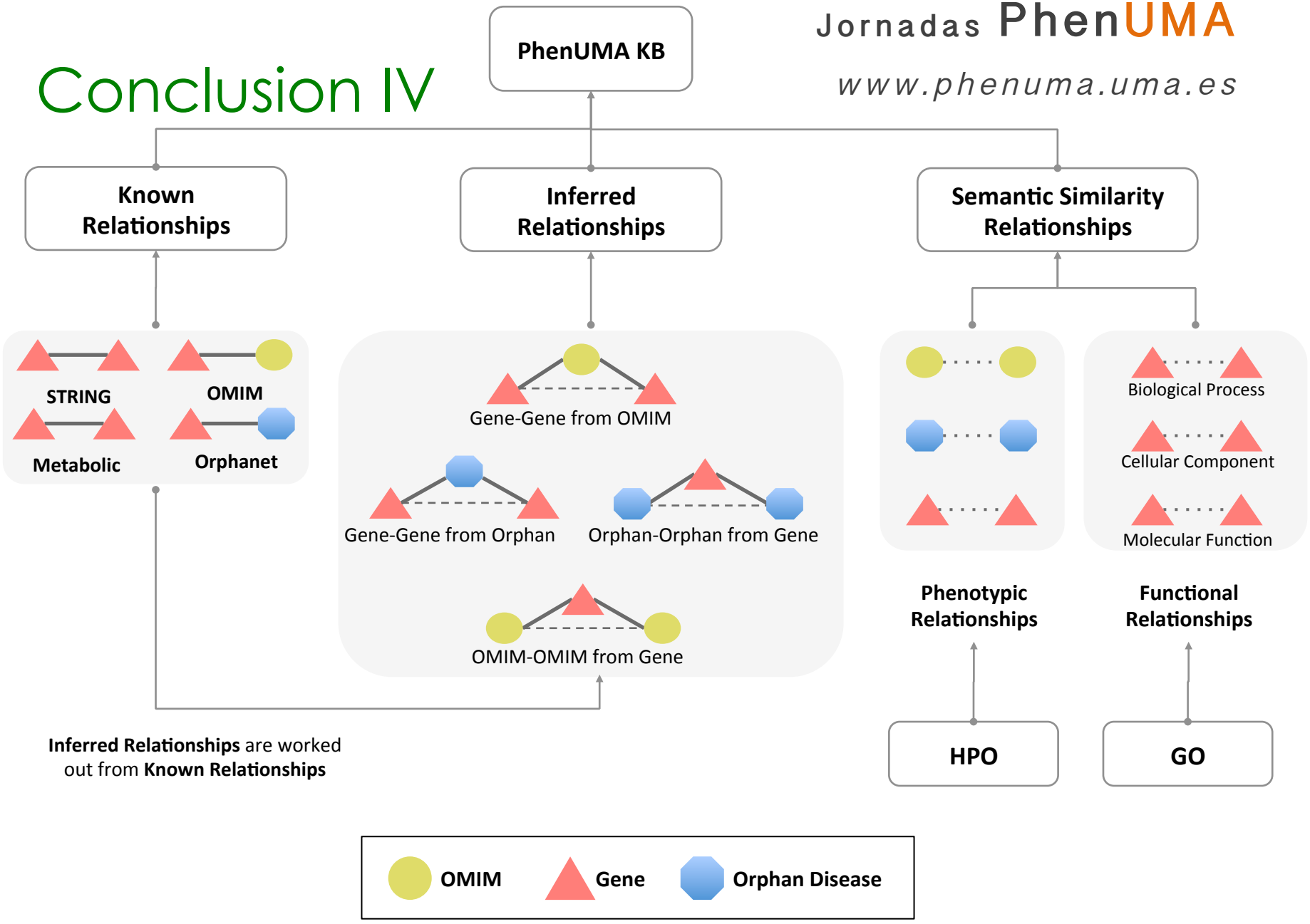
COHERENCIA BIOLÓGICA



Conclusion IV

Jornadas PhenUMA

www.phenuma.uma.es



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¡¡Muchas Gracias y Bienvenidos!!

Kika

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