

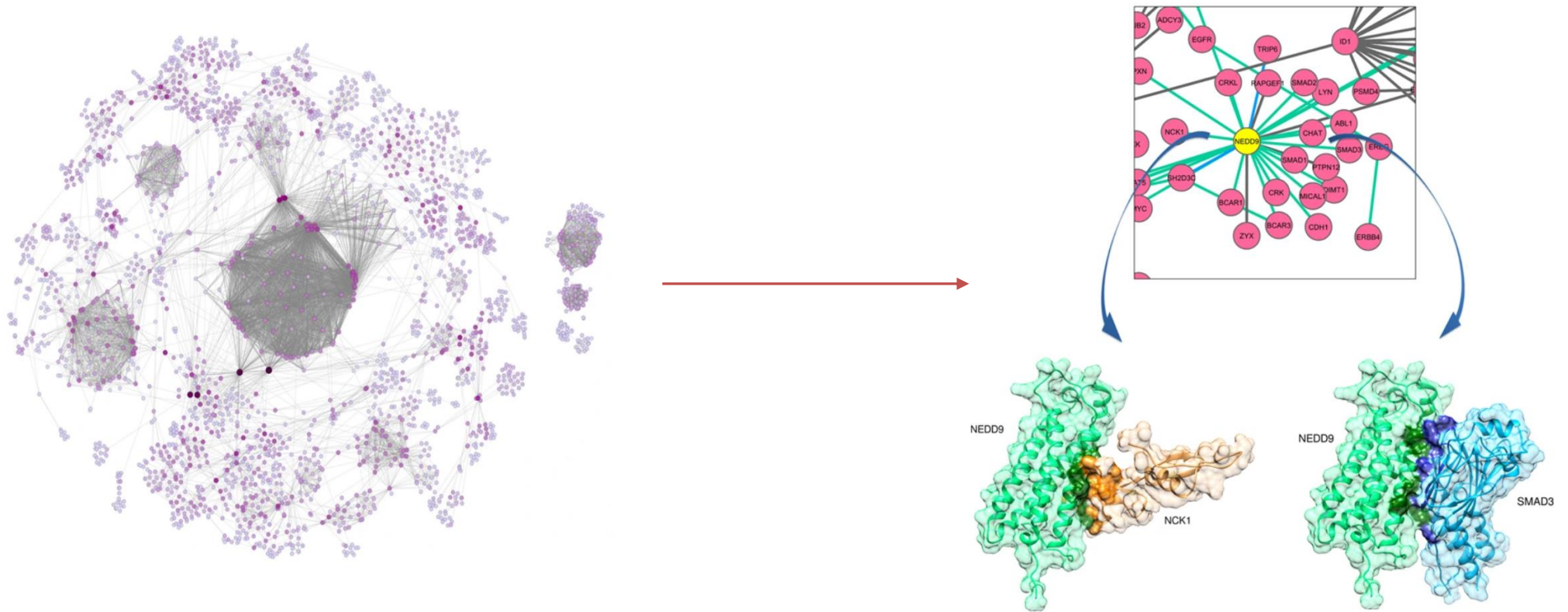
# Prediction of the Function of Protein Interactions in Post-Translational Modifications

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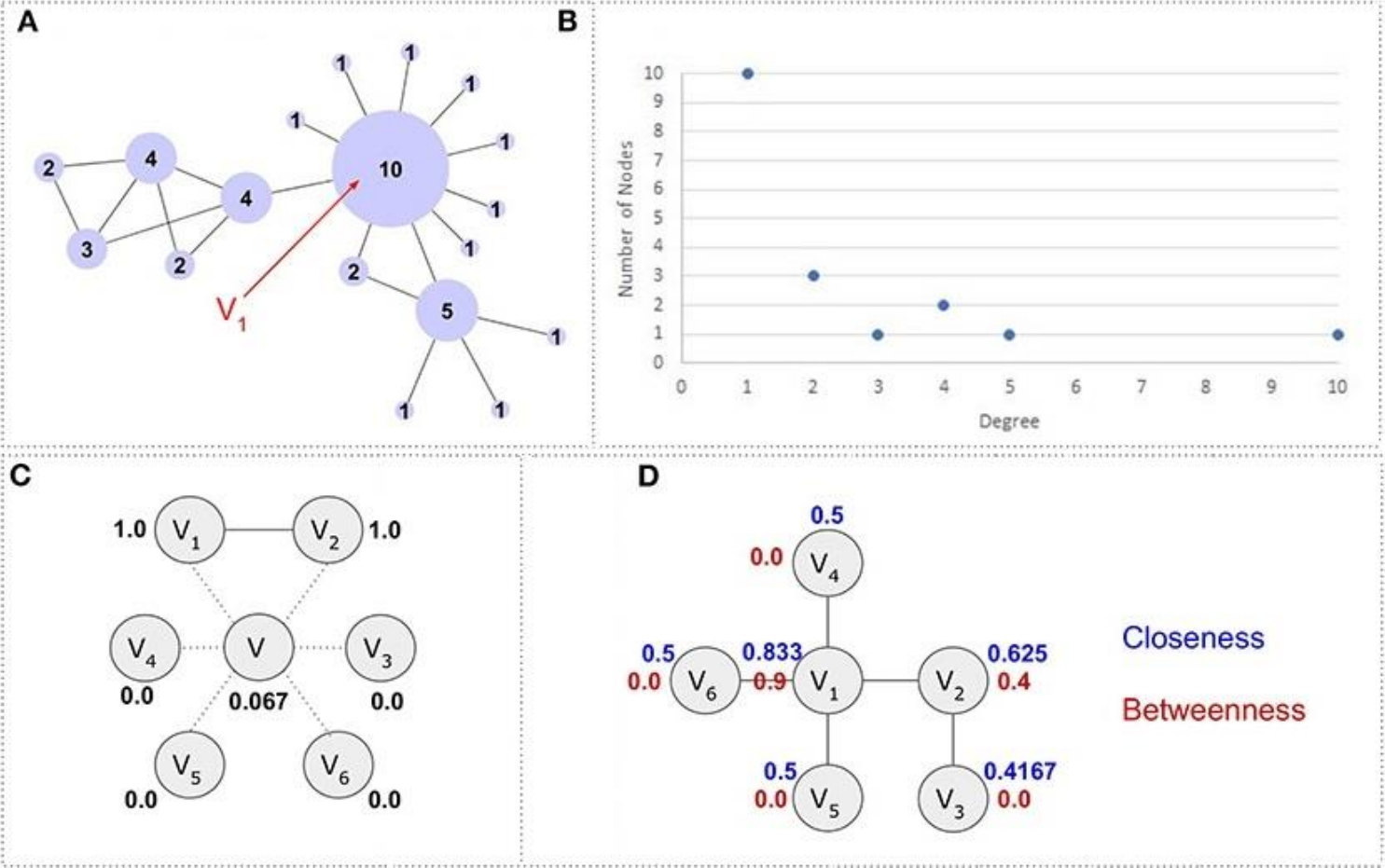
2023 M.Sc. Biology & Biomedicine  
Module: Proteinbiochemie und Bioinformatik

Aimilia Christina Vagiona  
PhD student  
Supervisor: Miguel Andrade

# Why do we study the human interactome?

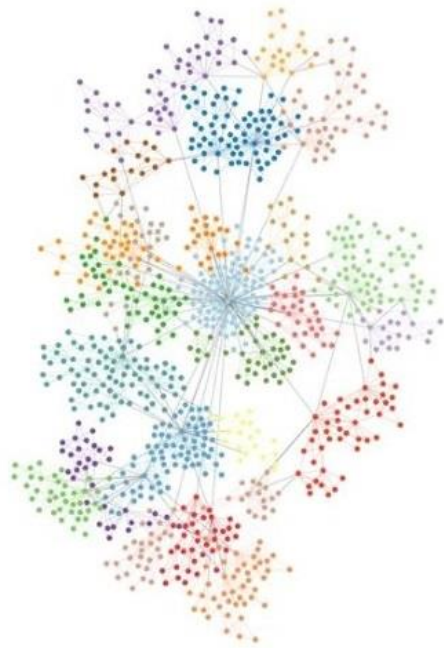


# Network theory

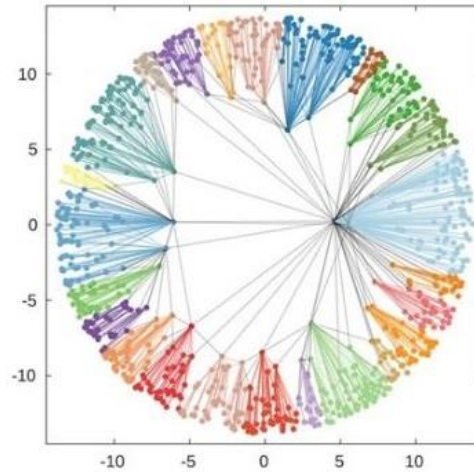


# Hyperbolic network model

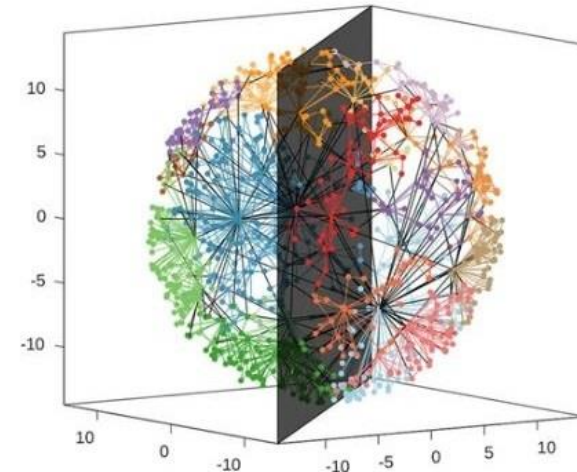
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Euclidean

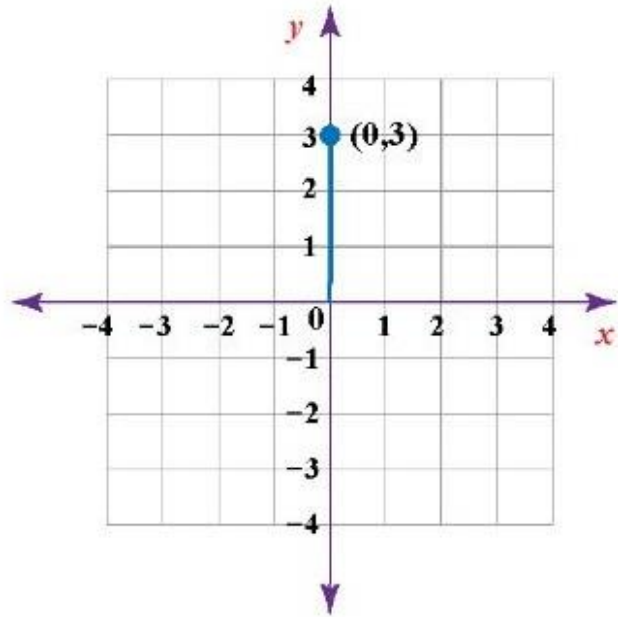


Hyperbolic PS model in 2D

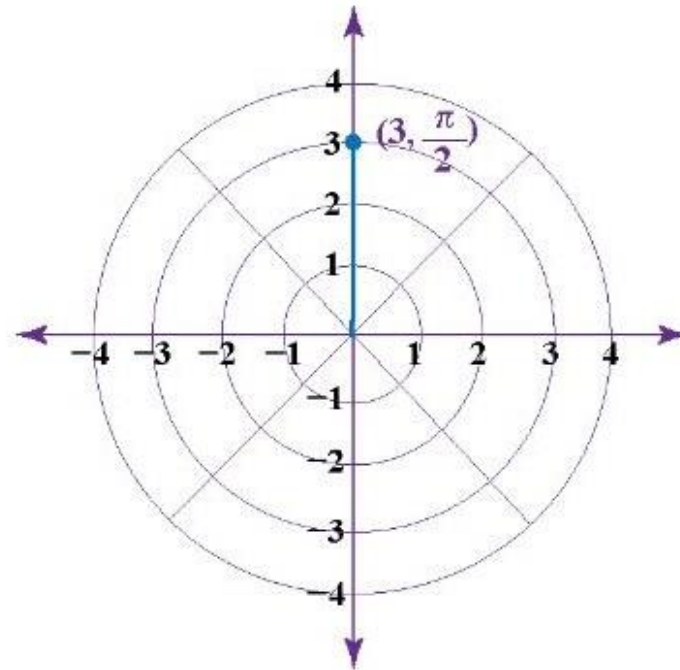


Hyperbolic PS model in 3D

# PS model



Euclidean Coordinates (x, y)



Polar Coordinates (r, theta)

1) Node Sorting: Nodes are sorted in decreasing order by degree

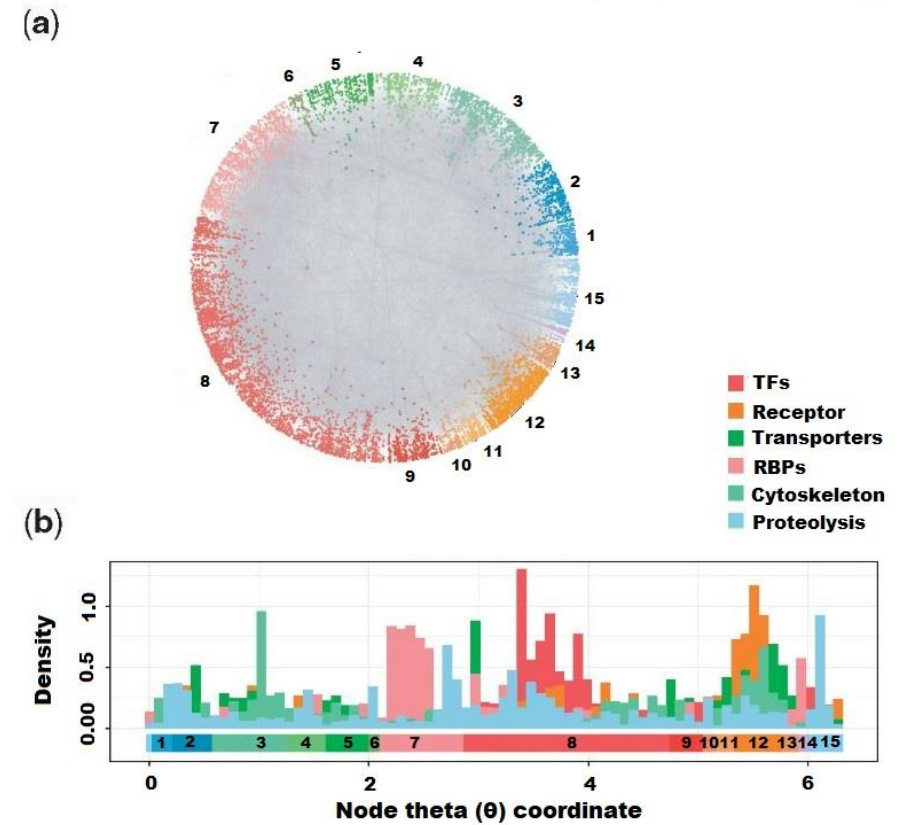
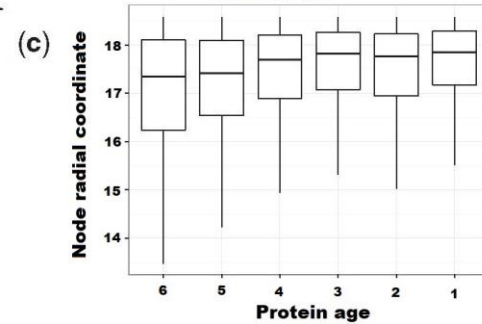
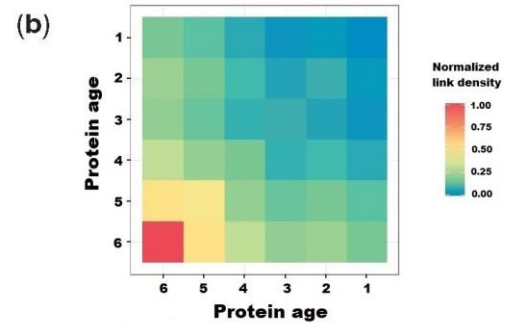
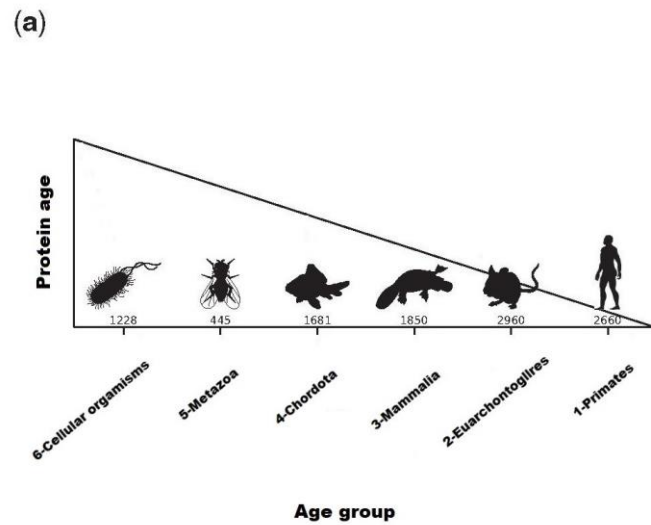
2) Starting Point: The first node is placed at the center and it gets a random angle

3) Expanding the Space: embedding new nodes:

- Distance from Center: in the new node assigned radial coordinate  $r_i = 2 \ln i$
- Adjusting Positions: The positions of existing nodes are adjusted based on their distances from the new node ( $r_j(i) = \beta r_j + (1 - \beta) r_i$ )
- Finding the Best Angle: The new node is given an angular coordinate that maximizes the likelihood of the PS model

4) Repeat for All Nodes: Steps 2 and 3 are repeated for every node in the network.

# hPIN in the Hyperbolic Space

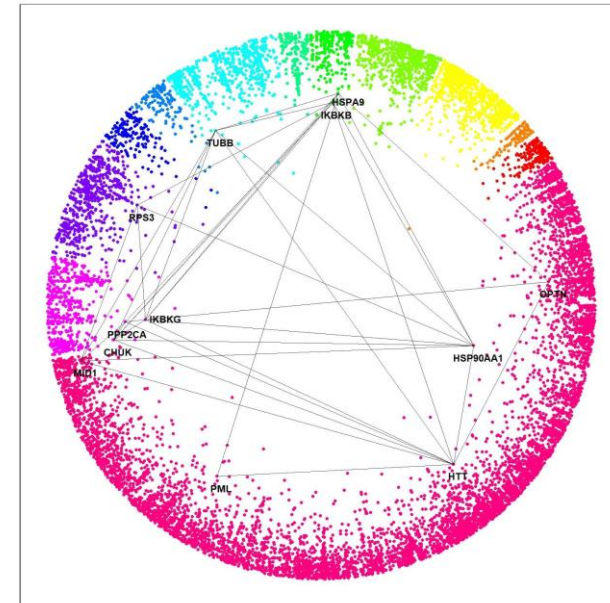
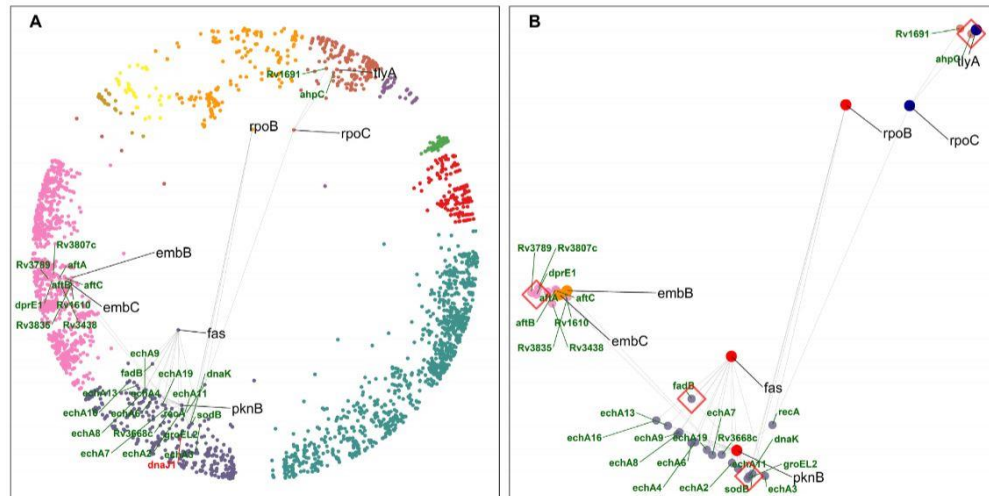


# hPIN in the Hyperbolic Space

Article

## Selection of Multi-Drug Targets against Drug-Resistant *Mycobacterium tuberculosis* XDR1219 Using the Hyperbolic Mapping of the Protein Interaction Network

Noor ul Ain Zahra <sup>1,2</sup>, Aimilia-Christina Vagiona <sup>2</sup>, Reaz Uddin <sup>1,\*</sup> and Miguel A. Andrade-Navarro <sup>2,\*</sup>



Article

## Analysis of Huntington's Disease Modifiers Using the Hyperbolic Mapping of the Protein Interaction Network

Aimilia-Christina Vagiona <sup>1</sup>, Pablo Mier <sup>1</sup>, Spyros Petrakis <sup>2</sup> and Miguel A. Andrade-Navarro <sup>1,\*</sup>

# Hyperbolic applications

---

[nature](#) > [scientific reports](#) > [articles](#) > [article](#)

Article | [Open access](#) | [Published: 06 August 2021](#)

## The inherent community structure of hyperbolic networks

[Bianka Kovács](#) & [Gergely Palla](#) 

[Scientific Reports](#) **11**, Article number: 16050 (2021)

[nature](#) > [nature communications](#) > [articles](#) > [article](#)

Article | [Open access](#) | [Published: 05 May 2021](#)

## Deep generative model embedding of single-cell RNA-Seq profiles on hyperspheres and hyperbolic spaces




[Jiarui Ding](#)  & [Aviv Regev](#) 

[Nature Communications](#) **12**, Article number: 2554 (2021) | [Cite this article](#)

IEEE TRANSACTIONS ON PATTERN ANALYSIS AND MACHINE INTELLIGENCE, VOL. 44, NO. 12, DECEMBER 2022

10023

## Hyperbolic Deep Neural Networks: A Survey

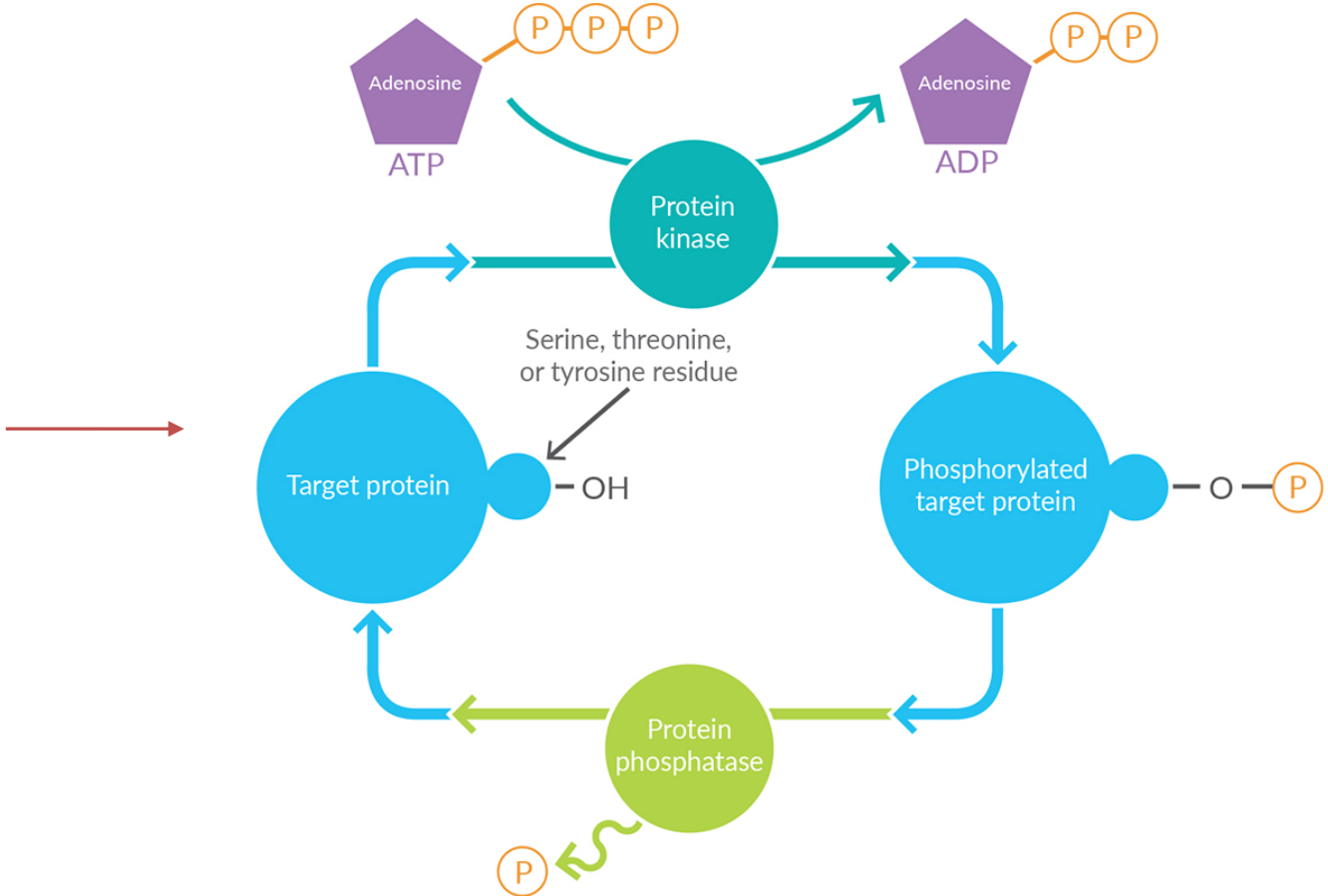
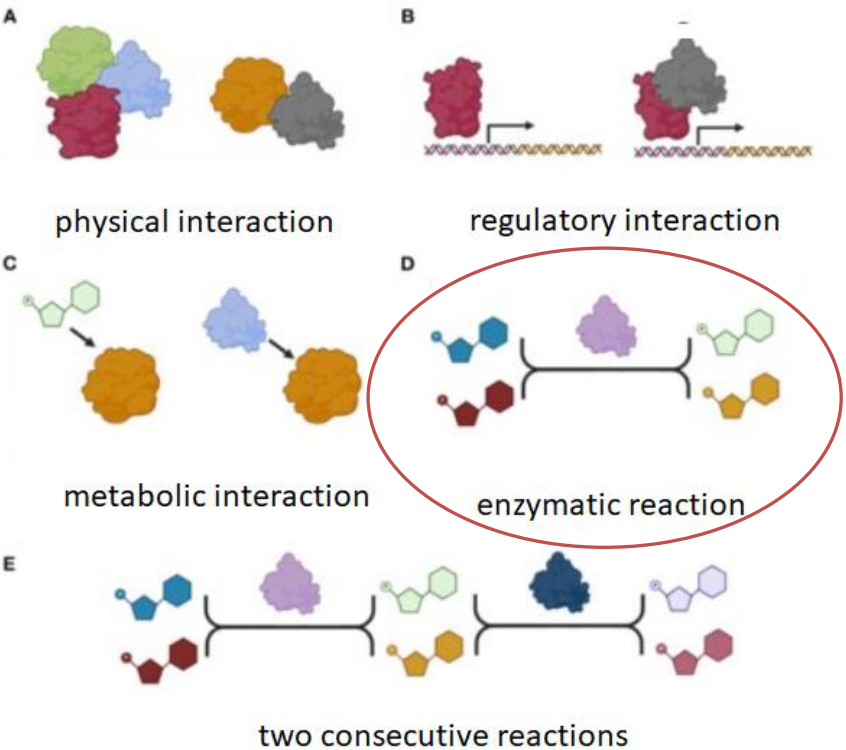
Wei Peng , Tuomas Varanka, Abdelrahman Mostafa,  
Henglin Shi , and Guoying Zhao , *Fellow, IEEE*

**Abstract**—Recently, hyperbolic deep neural networks (HDNNs) have been gaining momentum as the deep representations in the hyperbolic space provide high fidelity embeddings with few dimensions, especially for data possessing hierarchical structure. Such a hyperbolic neural architecture is quickly extended to different scientific fields, including natural language processing, single-cell RNA-sequence analysis, graph embedding, financial analysis, and computer vision. The promising results demonstrate its superior capability, significant compactness of the model, and a substantially better physical interpretability than its counterpart in the euclidean space. To stimulate future research, this paper presents a comprehensive review of the literature around the neural components in the construction of HDNN, as well as the generalization of the leading deep approaches to the hyperbolic space. It also presents current applications of various tasks, together with insightful observations and identifying open questions and promising future directions.

**Index Terms**—Neural networks on Riemannian manifold, hyperbolic neural networks, Poincaré model, Lorentz model



# Function of PPIs

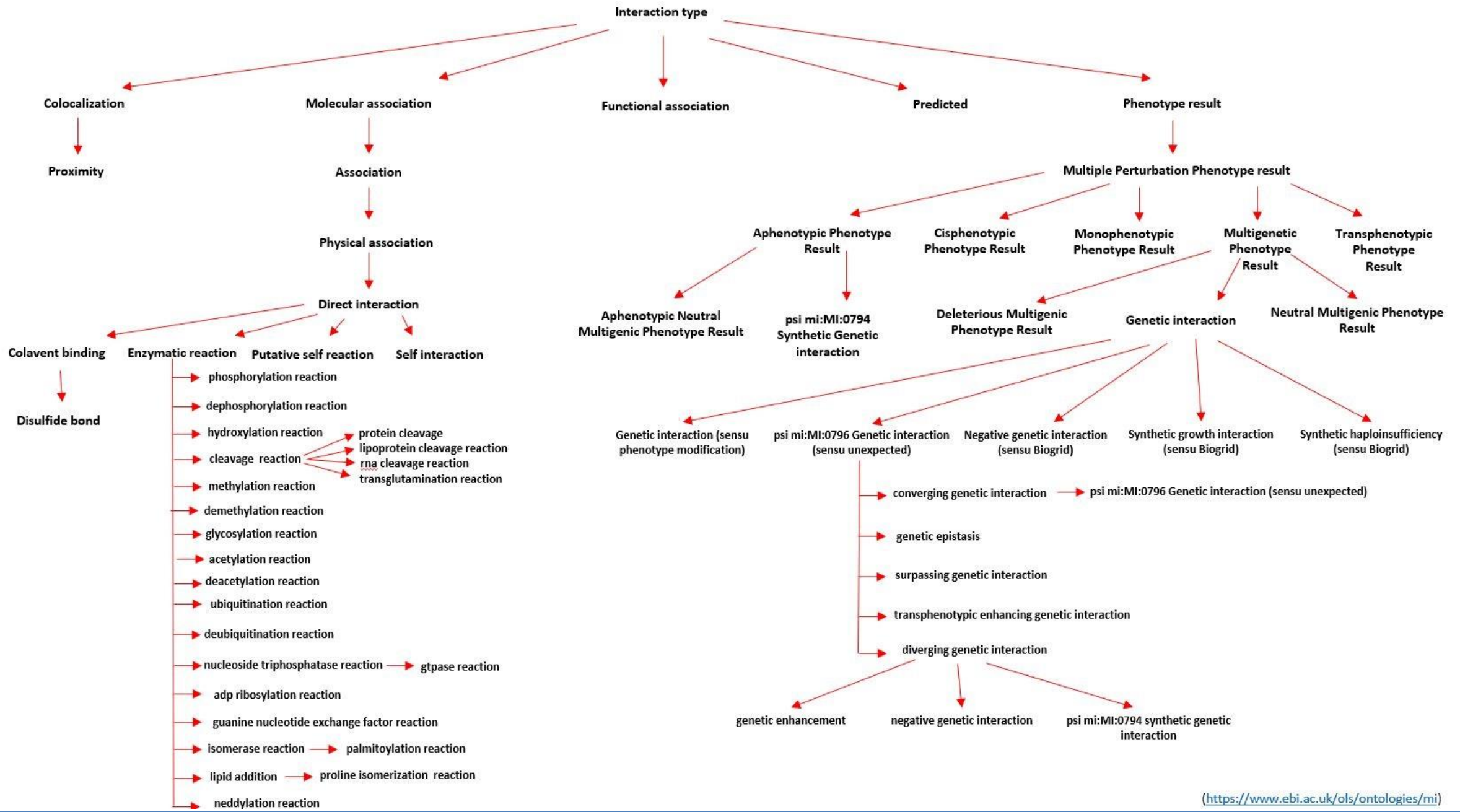


# Molecular annotations of PPIs

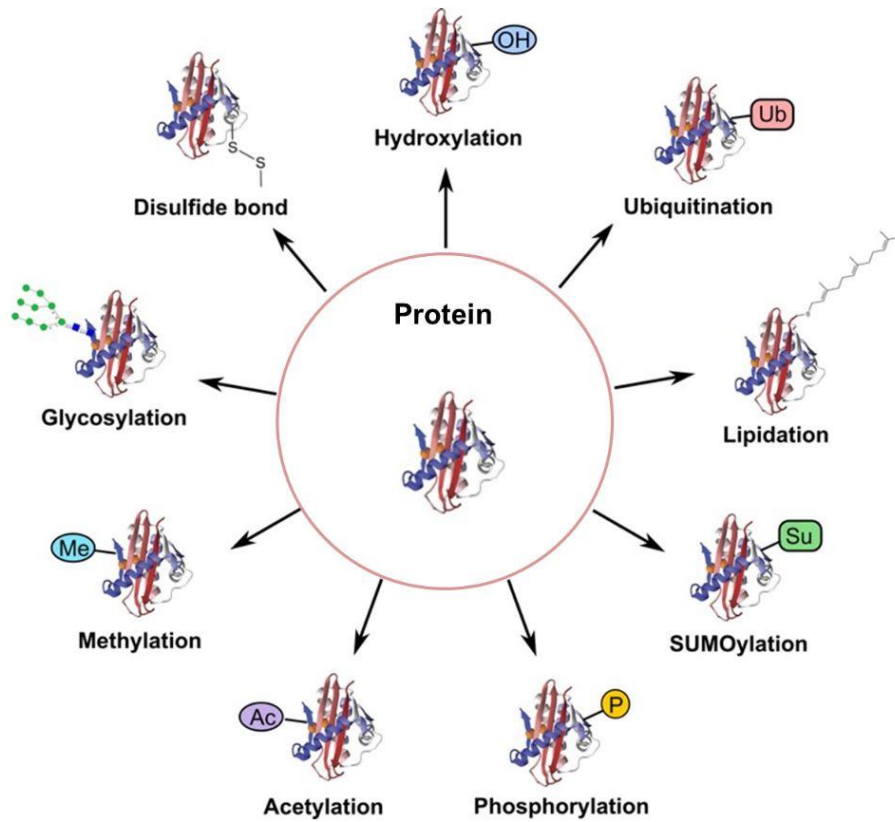
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The Molecular Interactions (MI) ontology forms a structured controlled vocabulary for the annotation of experiments concerned with protein-protein interactions.





# Why do we focus on PTMs?



## Roles of Post-translational Modifications in Spinocerebellar Ataxias

Linlin Wan<sup>1</sup>, Keqin Xu<sup>1</sup>, Zhao Chen<sup>1</sup>, Beisha Tang<sup>1,2,3,4,5,6,7</sup> and Hong Jiang<sup>1,2,3,4,8\*</sup>

<sup>1</sup> Department of Neurology, Xiangya Hospital, Central South University, Changsha, China, <sup>2</sup> National Clinical Research Center for Geriatric Diseases, Central South University, Changsha, China, <sup>3</sup> Key Laboratory of Hunan Province in Neurodegenerative Disorders, Central South University, Changsha, China, <sup>4</sup> Laboratory of Medical Genetics, Central South University, Changsha, China, <sup>5</sup> Parkinson's Disease Center of Beijing Institute for Brain Disorders, Beijing, China, <sup>6</sup> Collaborative Innovation Center for Brain Science, Shanghai, China, <sup>7</sup> Collaborative Innovation Center for Genetics and Development, Shanghai, China, <sup>8</sup> Department of Neurology, Xinjiang Medical University, Urumqi, China

Review

## Do Post-Translational Modifications Influence Protein Aggregation in Neurodegenerative Diseases: A Systematic Review

Larissa-Nele Schaffert<sup>1</sup> and Wayne G. Carter<sup>1\*</sup>

School of Medicine, University of Nottingham, Royal Derby Hospital Centre, Uttometer Road, Derby DE22 3DT, UK; larissaschaffert@yahoo.de

\* Correspondence: Wayne.Carter@nottingham.ac.uk; Tel.: +44-(0)1332-724738

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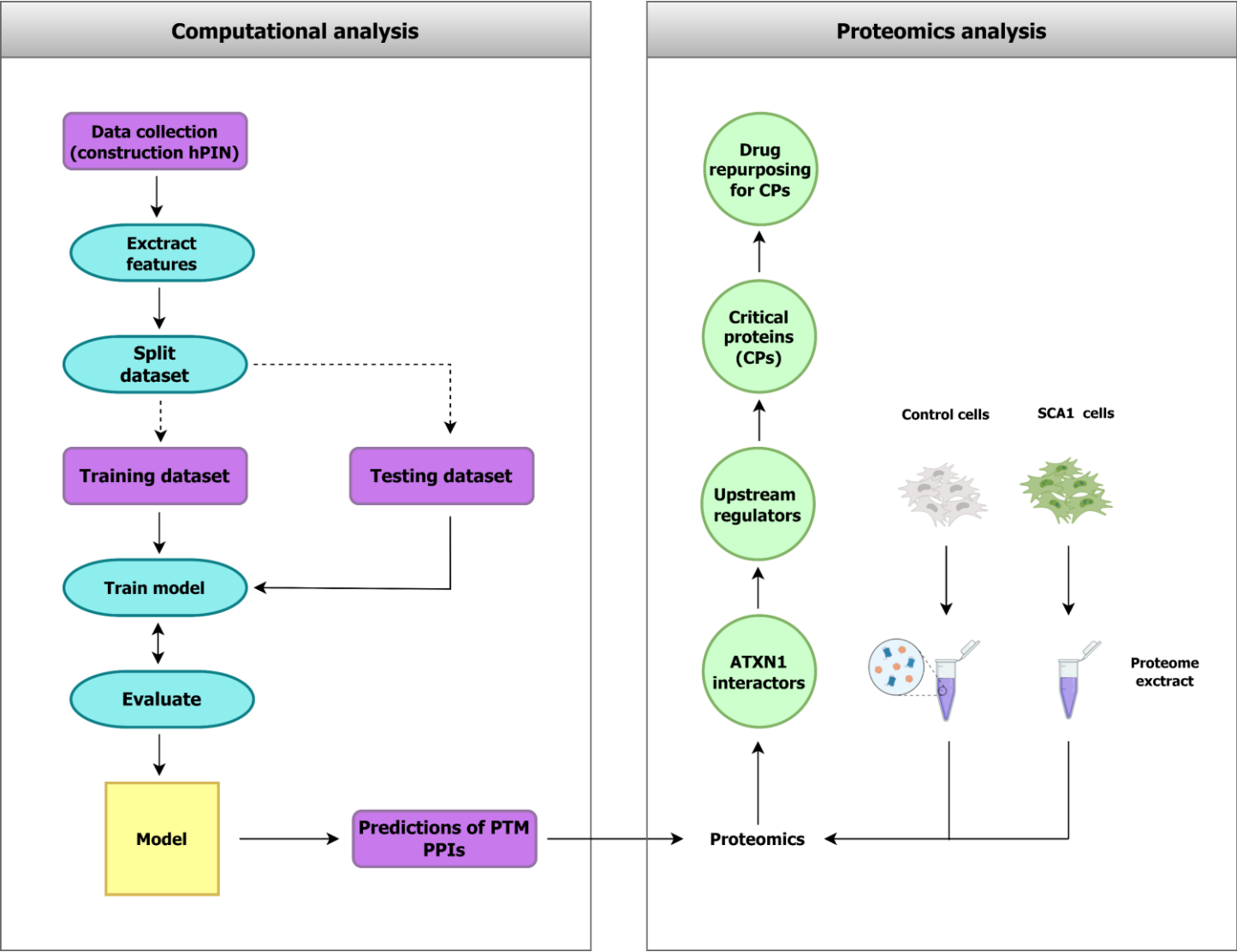
Review

## Post-translational modifications: Regulators of neurodegenerative proteinopathies

Rohan Gupta<sup>1</sup>, Mehar Sahu<sup>1</sup>, Devesh Srivastava<sup>1</sup>, Swati Tiwari<sup>1</sup>, Rashmi K. Ambasta, Pravir Kumar<sup>\*</sup>

Molecular Neuroscience and Functional Genomics Laboratory, Department of Biotechnology, Delhi Technological University (Formerly DCE), Delhi 110042, India

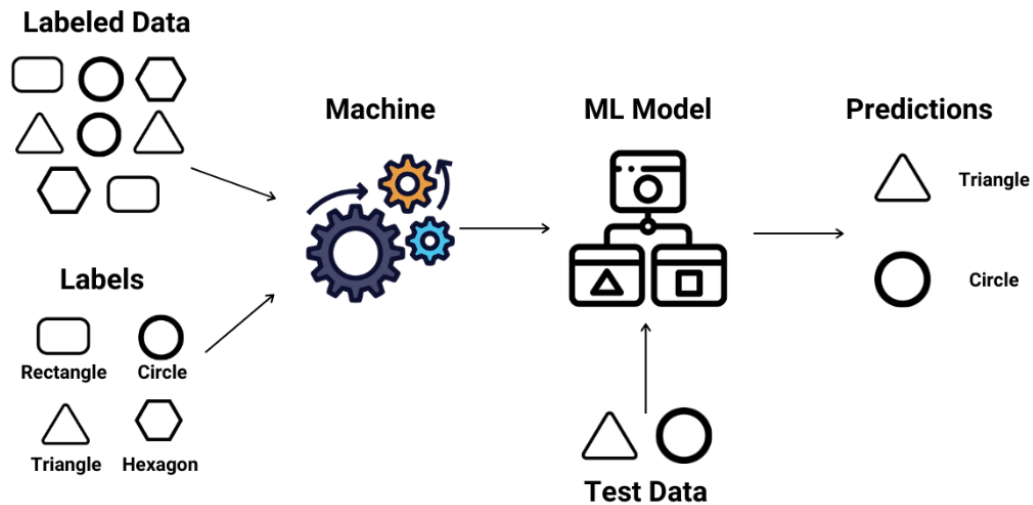




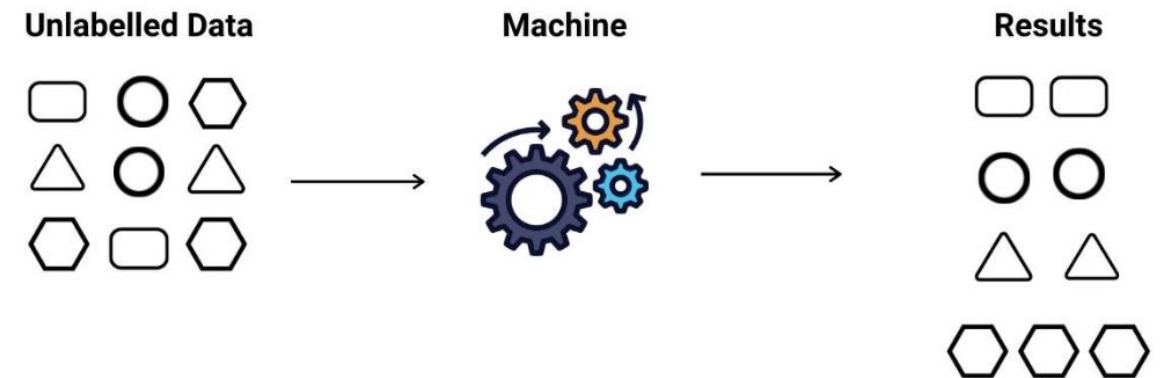
# What is machine learning?

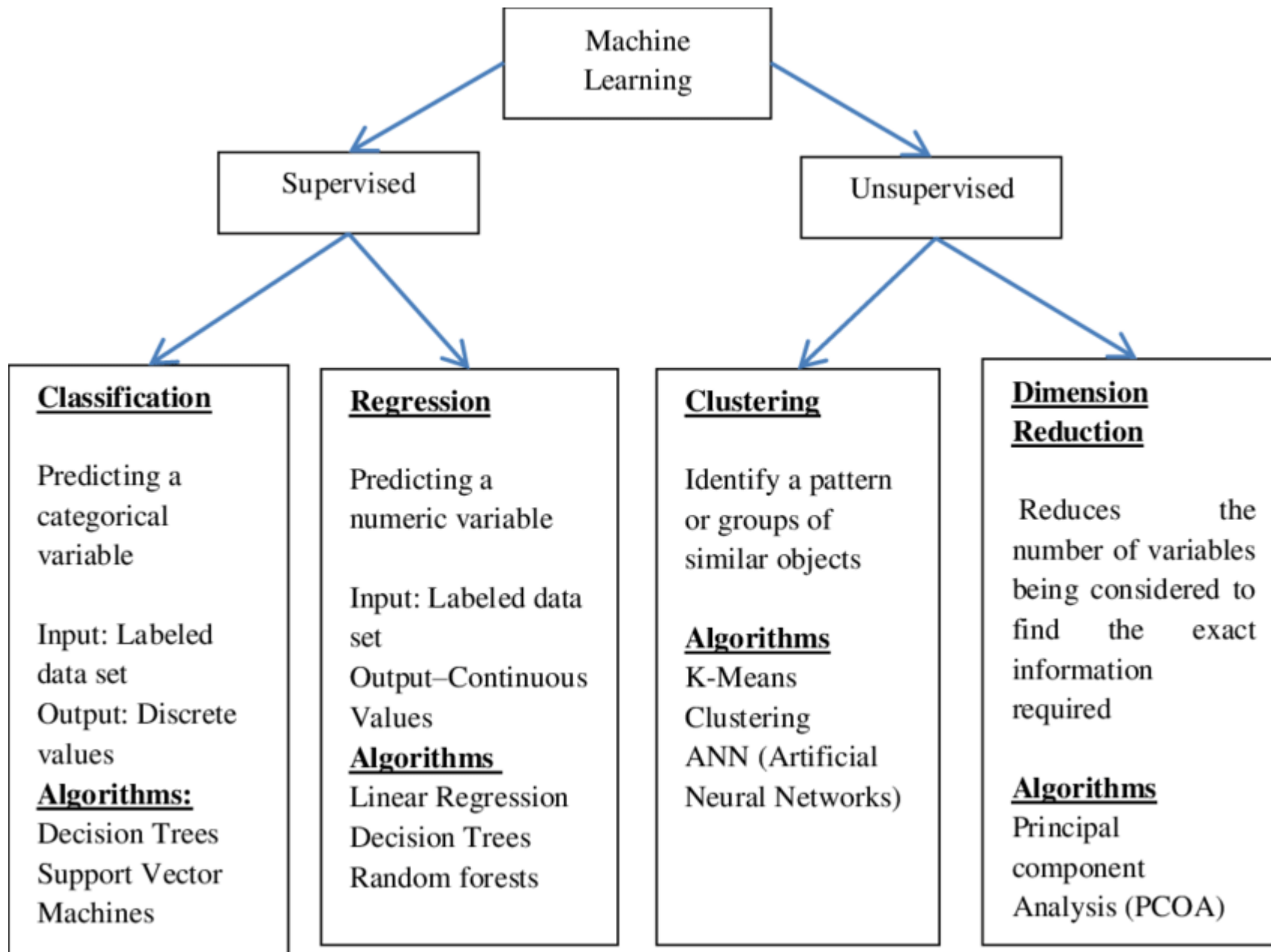
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## Supervised Learning



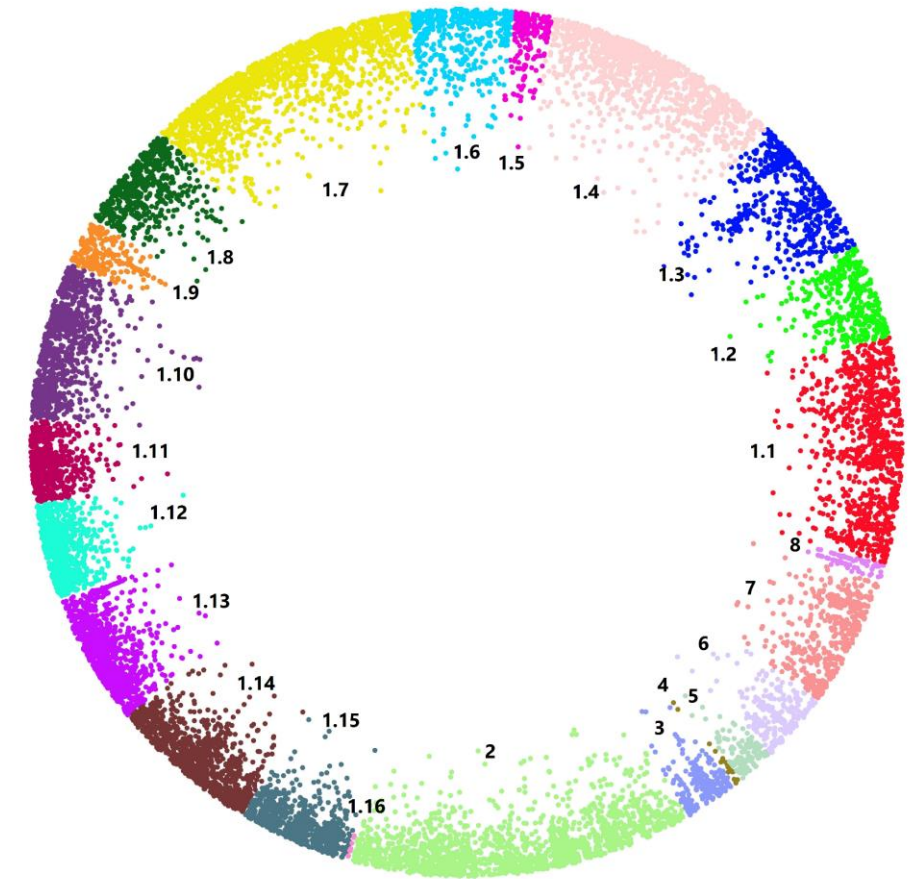
## Unsupervised Learning





# Features

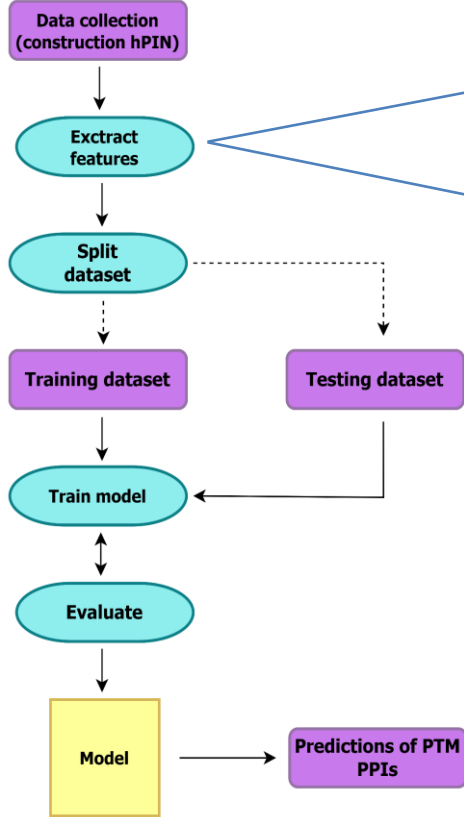
A



B

Cluster	GO BP Terms	Cluster	GO BP Terms
1.1	mRNA processing	1.13	mitochondrial translational elongation
1.2	regulation of gene silencing by miRNA	1.14	mitochondrial respiratory chain complex assembly
1.3	regulation of nucleobase-containing compound metabolic process	1.15	sphingolipid metabolic process
1.4	alpha-amino acid biosynthetic process	1.16	regulation of angiotensin levels in blood
1.5	cell cycle G1/S phase transition	2	regulation of cell cycle G2/M phase transition
1.6	post-translational protein modification	3	intracellular retrograde transport
1.7	protein ubiquitination	4	N-terminal protein amino acid modification
1.8	positive regulation of establishment of protein localization to telomere	5	positive regulation of tyrosine phosphorylation of STAT protein
1.9	regulation of cellular amine metabolic process	6	positive regulation of lipopolysaccharide-mediated signaling pathway
1.10	metanephric renal vesicle morphogenesis	7	chemokine-mediated signaling pathway
1.11	protein transport	8	regulation of DNA-templated transcription, initiation
1.12	protein insertion into ER membrane by stop-transfer membrane-anchor sequence		

## Computational analysis



Degree Centrality



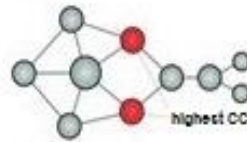
Betweenness Centrality



Eigenvector Centrality

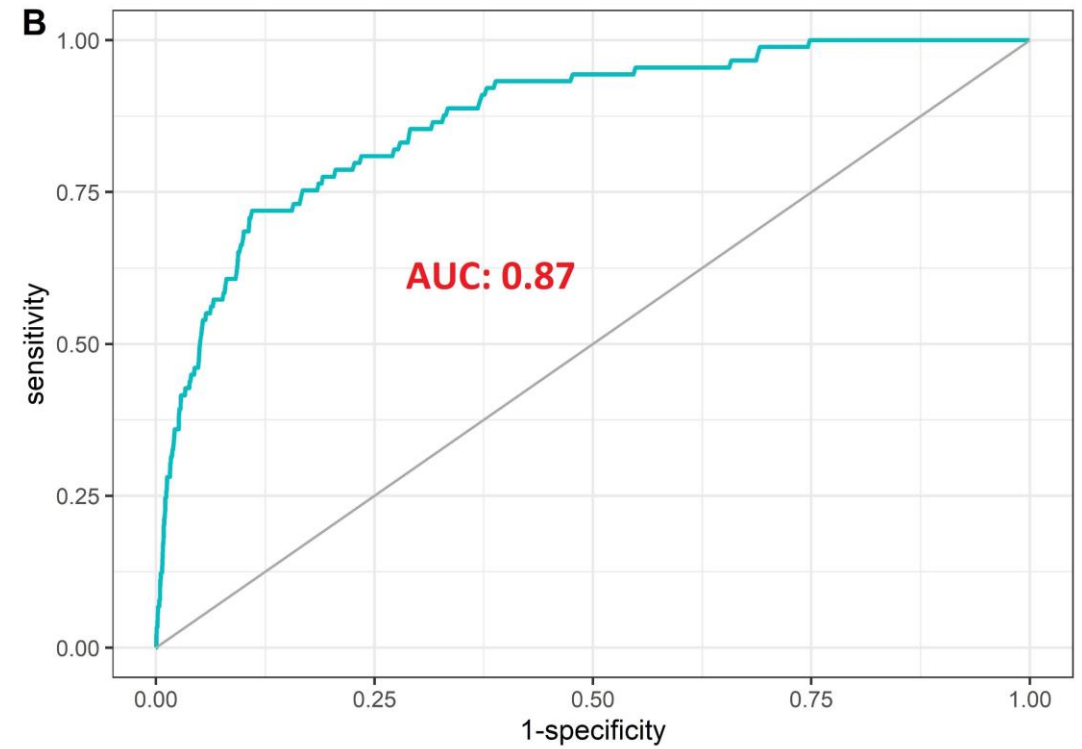
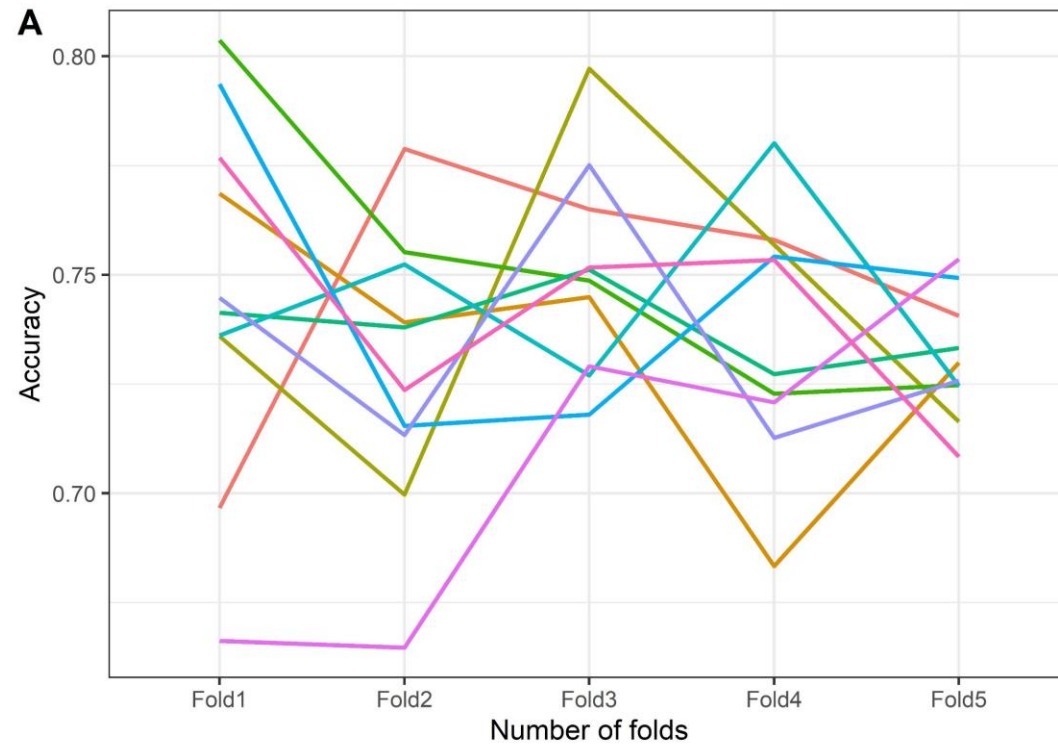


Closeness Centrality

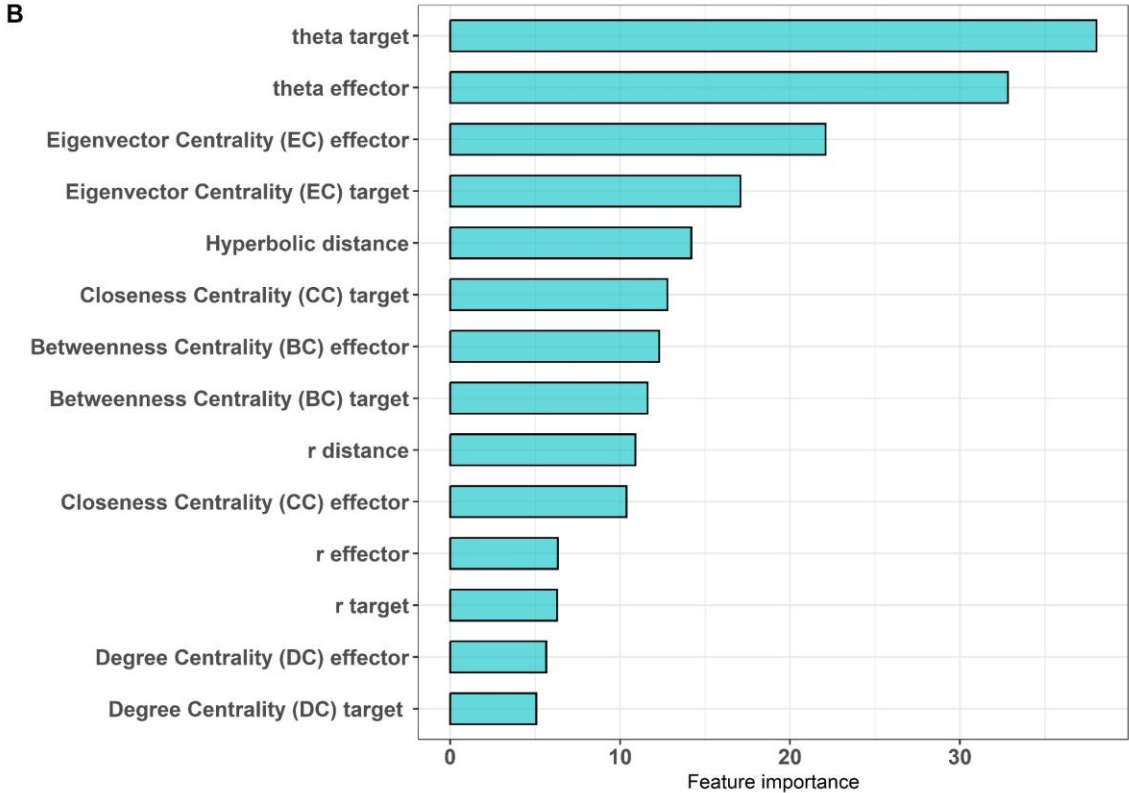
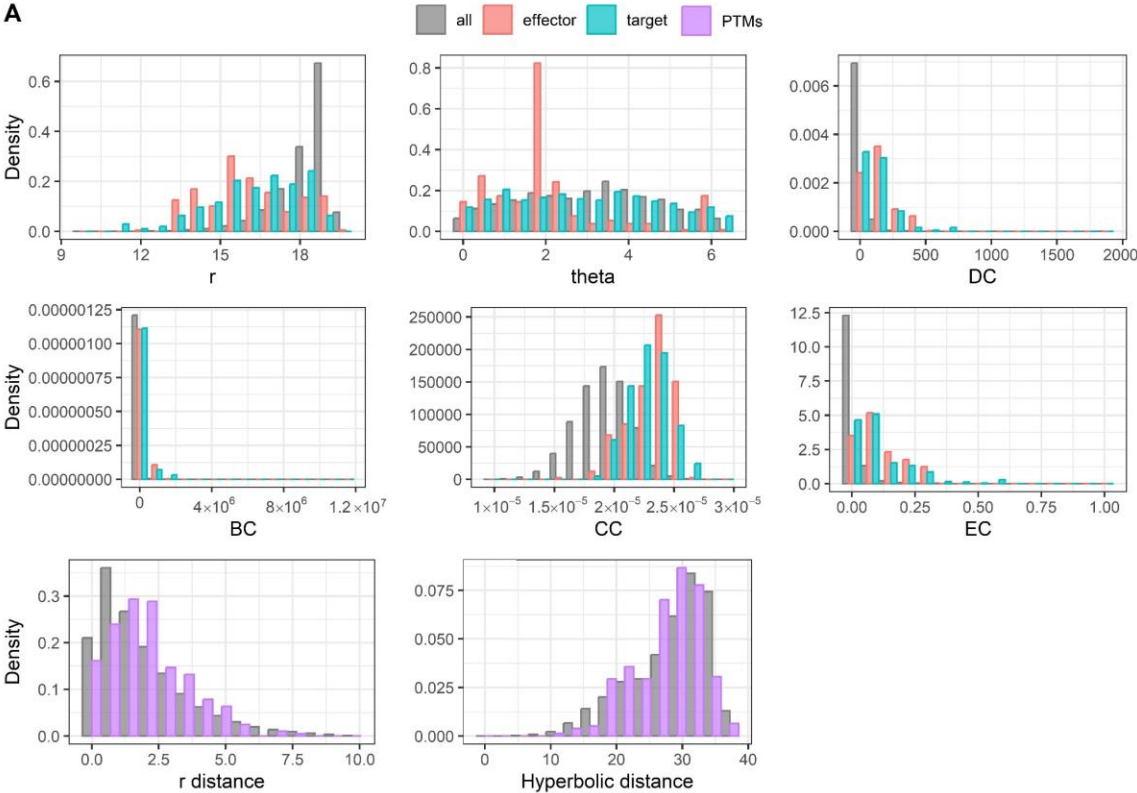




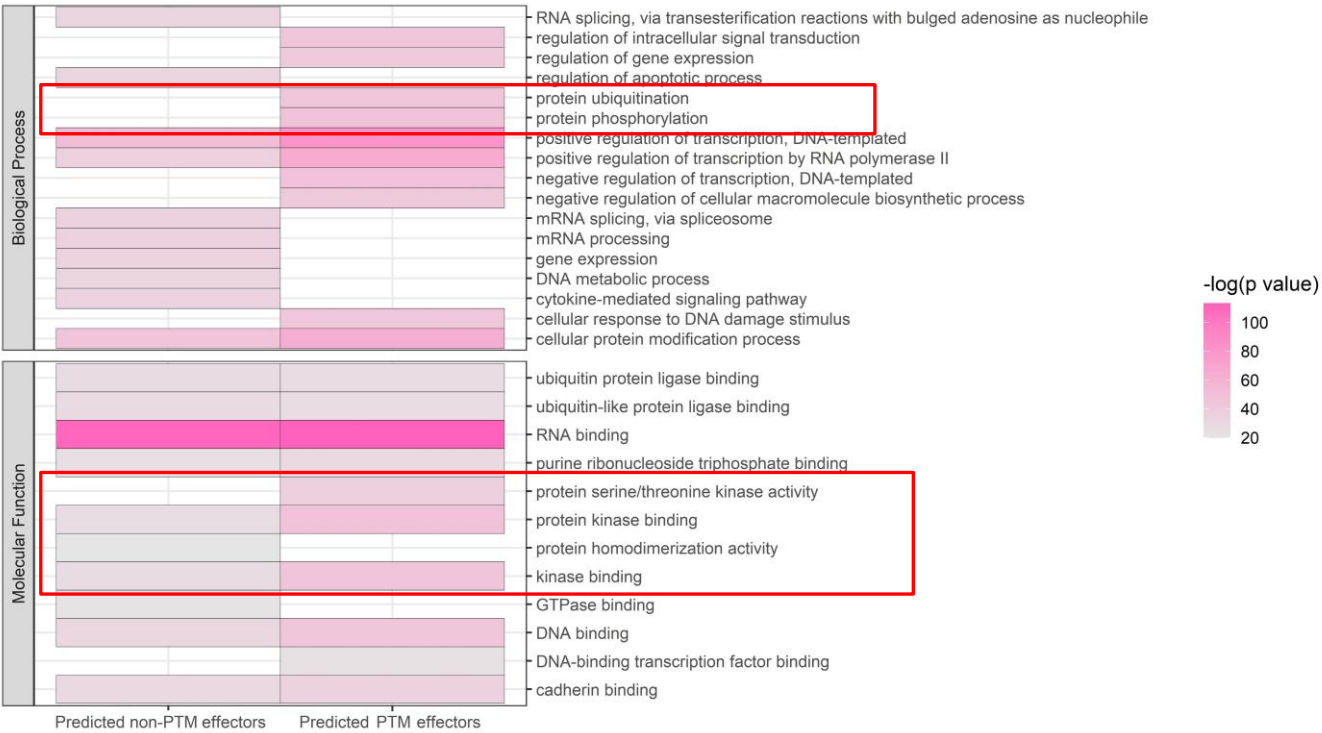
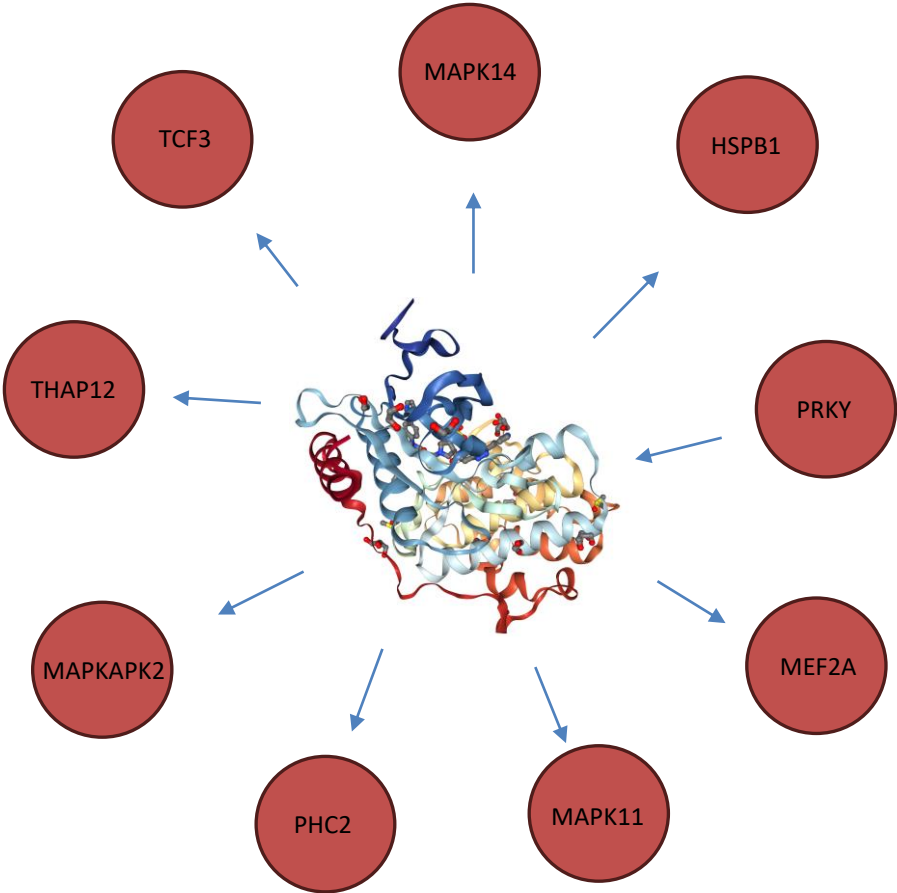
# RF model



# Feature importance

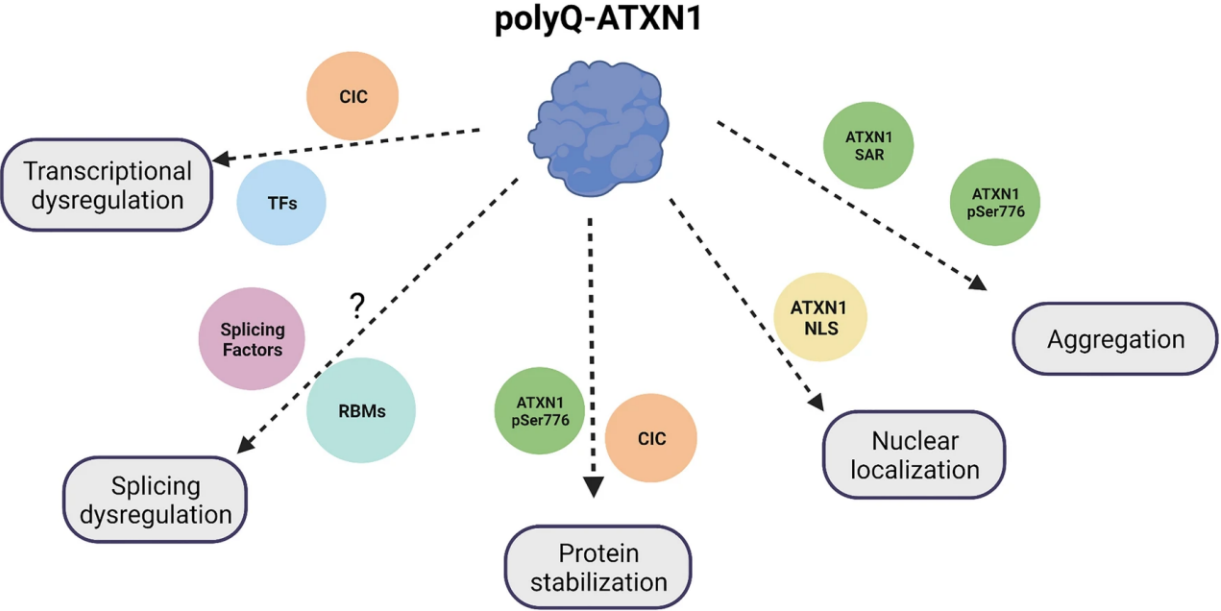
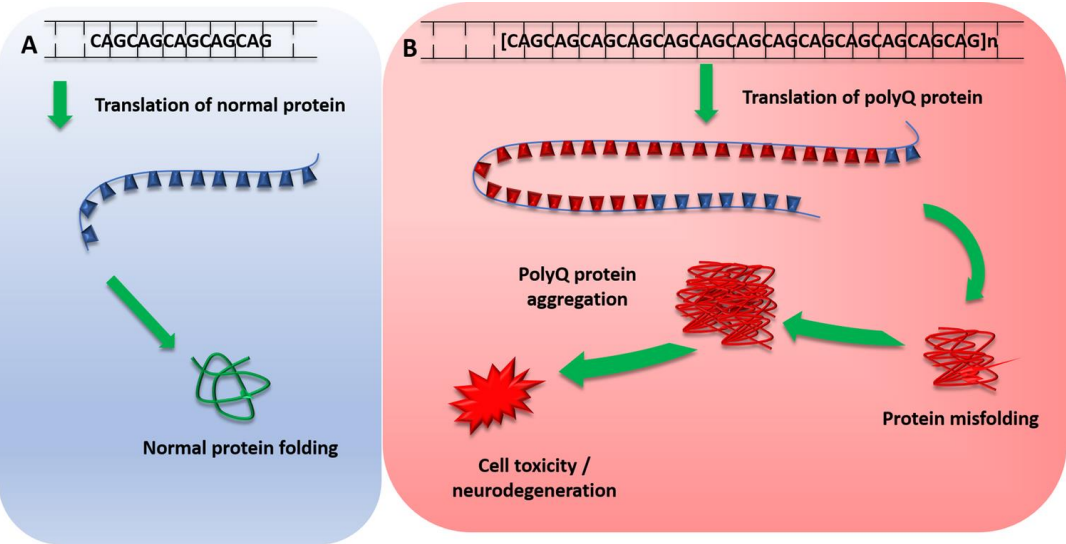


# MAPK3 protein kinase

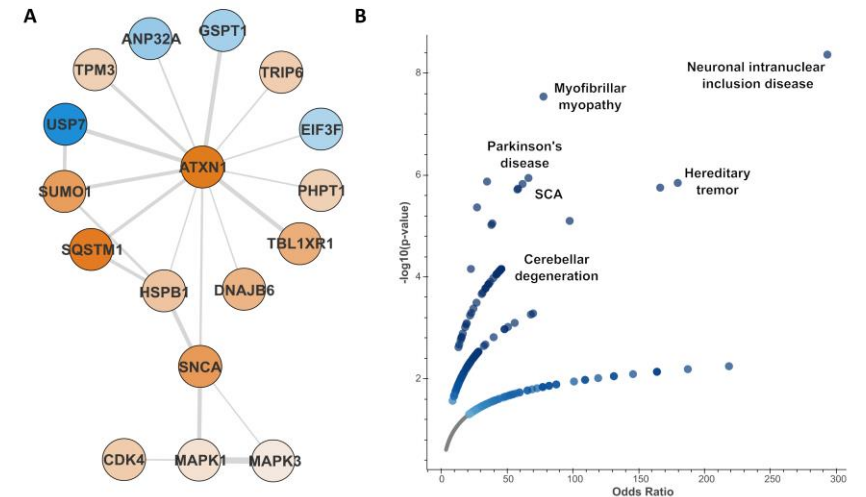
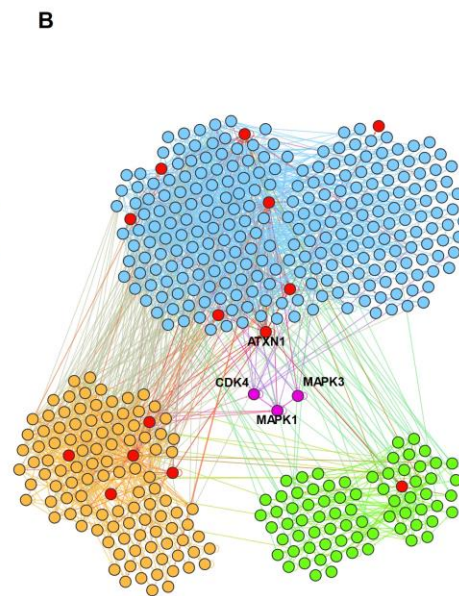
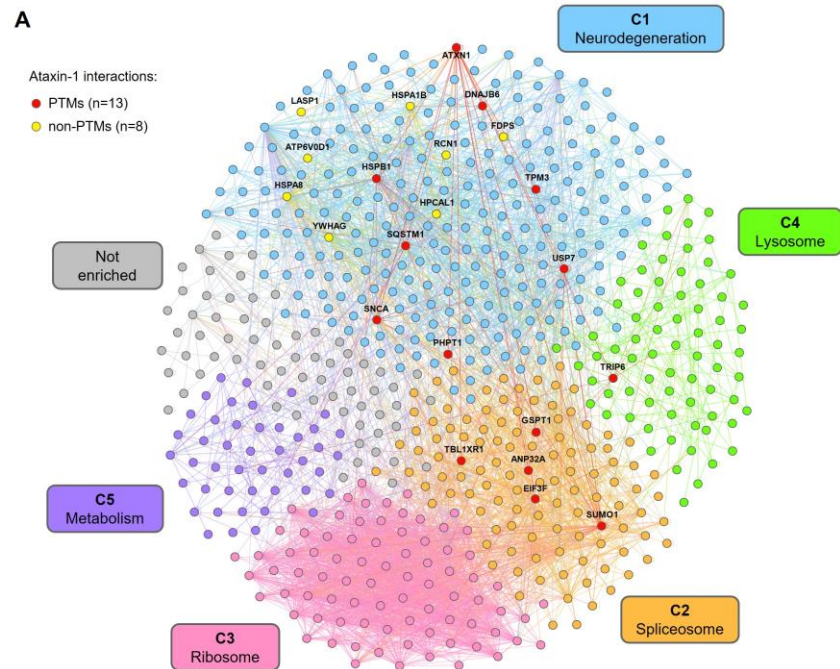


# Spinocerebellar ataxia 1 (SCA1)

## Molecular mechanisms of SCA1 pathogenesis



# SCA1 cell model- Predicted PTMs



**C**

Drug candidate	Reverse score	Administration
artesunate	25%	Malaria
BRD-K54687541	25%	Unknown
betamethasone	25%	cerebral edema, congenital adrenal hyperplasia
budesonide	25%	Crohn's disease, asthma, allergies
BRD-K71265179	25%	Unknown
Linifanib	25%	hematologic malignancies, solid tumors
BRD-A08662020	25%	Unknown

# Next steps

---

Experimental validation  
of the predicted directed PTMs



Experimental verification of the  
suggested drugs



Explore hyperbolic geometry  
in different biological data



# References

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# Acknowledgments

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Lovely to meet you all !!!!!

---

Thank you!  
Any questions?

# Let's play...



**HIPPIE** » Human Integrated Protein-Protein Interaction rEference

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Welcome to HIPPIE, a web tool to generate reliable and meaningful human protein-protein interaction networks

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(e.g. HD\_HUMAN, P42858, HTT or 3064)

Here, you can query HIPPIE for the interaction partners of a single protein ↗  
Or check out further [query options and examples](#)

**NEWS**

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- Feb 14, 2019** A new version of HIPPIE (v2.2) has been released today
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Input: one protein

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Construction of a HIPPIE subnetwork from an input query set of proteins or interactions

**Query set**

**Input a list of proteins/interactions**

Example input: dnmt3a dnmt3b

Alternatively, choose a file to upload  No file chosen

(this may take a while)

**Output parameters**

**Output type**

**Min. number of PPIs to query set**  [1,Inf]

**Score filter (optional)** Insert a threshold on the HIPPIE confidence score  [0,1] Or, choose predefined confidence level

**Interaction type filter (optional)**

Association (MI:0914)

Physical association (MI:0915)

Direct interaction (MI:0407)

Colocalization (MI:0403)

None

Adipose - Subcutaneous

Adipose - Visceral (Omentum)

Adrenal Gland

**Input of user defined filter set**

Input: list of protein

# How many interactors ATXN1 has?

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Search: ATXN1

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Search results for [ATX1\\_HUMAN](#) / [6310](#) / ATXN1

[Visualize this subnetwork.](#)  
 See [diseases](#), [biological processes](#), [molecular functions](#) or [cellular compartments](#) significantly associated with proteins in this subnetwork.

Copy table content Export to TSV Show 50 entries Search:

interactor - UniProt id	interactor - Entrez gene id	interactor - gene symbol	score (click on a score value to see the evidence)	Interacting proteins
<a href="#">1433E_HUMAN</a>	<a href="#">7531</a>	YWHAE	<a href="#">0.90</a>	<a href="#">Show</a>
<a href="#">1433Z_HUMAN</a>	<a href="#">7534</a>	YWHAZ	<a href="#">0.90</a>	<a href="#">Show</a>
<a href="#">ATX1_HUMAN</a>	<a href="#">6310</a>	ATXN1	<a href="#">0.89</a>	<a href="#">Show</a>
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<a href="#">TBL1R_HUMAN</a>	<a href="#">79718</a>	TBL1XR1	<a href="#">0.86</a>	<a href="#">Show</a>
<a href="#">UBP7_HUMAN</a>	<a href="#">7874</a>	USP7	<a href="#">0.86</a>	<a href="#">Show</a>
<a href="#">CA094_HUMAN</a>	<a href="#">84970</a>	C1orf94	<a href="#">0.85</a>	<a href="#">Show</a>
<a href="#">CRK_HUMAN</a>	<a href="#">1398</a>	CRK	<a href="#">0.85</a>	<a href="#">Show</a>

Interactors of ATXN1

confidence score

# How many interactors ATXN1 has with confidence score more than 0.71?

**HIPPIE** » Human Integrated Protein-Protein Interaction rEference

PROTEIN QUERY **NETWORK QUERY** BROWSE SCREEN ANNOTATION DOWNLOAD INFORMATION

Construction of a HIPPIE subnetwork from an input query set of proteins or interactions

Input a list of [proteins/interactions](#)

Query set

Example input: dnmt3a dnmt3b

Alternatively, choose a file to upload  
 No file chosen

(this may take a while)

Output parameters

**Output type**  
show in browser - visualization

**Layers**  
1 (between input and HIPPIE)

**Min. number of PPIs to query set**  
1 [1,inf]

**Score filter (optional)**  
Insert a threshold on the **HIPPIE confidence score**  
0.01 [0,1]

Or, choose predefined **confidence level**  
no filter

**Interaction type filter (optional)**

Association (MI:0914)  
 Physical association (MI:0915)  
 Direct interaction (MI:0407)  
 Colocalization (MI:0403)

None  
 Adipose - Subcutaneous  
 Adipose - Visceral (Omentum)  
 Adrenal Gland

Input of user defined filter set

Search: ATXN1

text

set to 0.71

# How many interactors ATXN1 has with confidence score more than 0.71 that are expressed in the cerebellum?

Query set  Example input: dnmt3a dnmt3b  No file chosen

(this may take a while)

Alternatively, choose a file to upload

Output parameters **Output type**  **Layers**  **Min. number of PPIs to query set**  [1,Inf]

**Score filter (optional)** Insert a threshold on the HIPPIE confidence score  [0,1] Or, choose predefined confidence level

**Interaction type filter (optional)**  Association (MI:0914)  Physical association (MI:0915)  Direct interaction (MI:0407)  Colocalization (MI:0403)

**Tissue filter (optional)**  None  Adipose - Subcutaneous  Adipose - Visceral (Omentum)  Adrenal Gland  Artery - Aorta  Artery - Coronary  Artery - Tibial  Bladder  Brain - Amygdala  Brain - Anterior cingulate cortex (BA24)  Brain - Caudate (basal ganglia)  Brain - Cerebellar Hemisphere  Brain - Cerebellum  Brain - Cortex  Brain - Frontal Cortex (BA9)  Brain - Hippocampus  in

**Input of user defined filter set**

Alternatively, choose a file to upload  No file chosen

**Functional filter (optional)** **GO (Gene ontology) (slim)**  biological\_process  cellular\_component **MeSH (Medical Subject Headings)**  Diseases

How many interactors ATXN1 has, with confidence score more than 0.71 that are expressed in the cerebellum and associated with neurodegenerative disease?

**Functional filter (optional)**

**GO (Gene ontology) (slim)**

- biological\_process
- cellular\_component
- cell
- extracellular\_region
- organelle
- protein\_complex

**LIVER\_DISEASES**

- Liver Diseases, Parasitic
- Lung Diseases
- Lung Diseases, Parasitic
- Lymphatic Diseases
- Mammary Neoplasms, Animal
- Marijuana Abuse
- Meningitis, Viral
- Mesomycetozoea Infections
- Metabolic Diseases
- Mink Viral Enteritis
- Mouth Diseases
- Multiple Trauma
- Muscular Diseases
- Muscular Dystrophy, Animal
- Musculoskeletal Abnormalities
- Mycoses
- Myxomatosis, Infectious
- Nasal Septal Perforation
- Neck Injuries
- Neonatal Abstinence Syndrome
- Neoplasms by Histologic Type
- Neoplasms by Site
- Neoplasms, Experimental
- Neoplasms, Hormone-Dependent
- Neoplasms, Multiple Primary
- Neoplasms, Post-Traumatic
- Neoplasms, Radiation-Induced
- Neoplasms, Second Primary
- Neoplastic Processes
- Neoplastic Syndromes, Hereditary
- Nervous System Malformations
- Nervous System Neoplasms
- Neurocutaneous Syndromes
- Neurodegenerative Diseases
- Neurologic Manifestations
- Neurotoxicity Syndromes
- Nose Diseases
- Nose Diseases
- Nutrition Disorders
- Occupational Injuries
- Ocular Hypertension
- Ocular Hypotension
- Ocular Motility Disorders
- Opioid-Related Disorders
- Opportunistic Infections
- Opportunistic Infections
- Optic Nerve Diseases
- Orbital Diseases
- Otorhinolaryngologic Neoplasms
- Pancreatic Diseases
- Paraneoplastic Syndromes
- Parasitemia
- Parasitic Diseases, Animal
- Parasitic Diseases, Animal
- Parathyroid Diseases
- Paratuberculosis
- Parturient Paresis
- Pathologic Processes
- Pathological Conditions, Anatomical
- Pelvic Floor Disorders
- Peritoneal Diseases
- Persian Gulf Syndrome