HIVE: a novel tool for Horizontal multi-omics Integration analysis using Variational AutoEncoders

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* Equal co-authors

Silvia Bottini, PhD
Junior professor chair INRAE

Statomique

Lille, 21st November 2023

The history of FMRP protein, a Multifunctional RNA-binding Protein

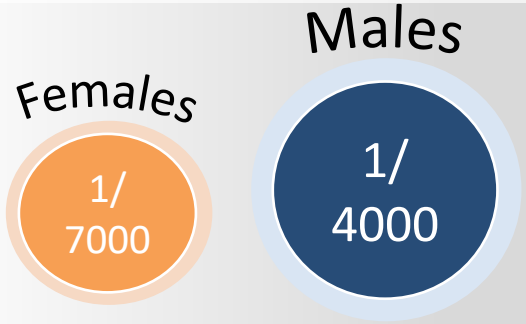
FMRP and the fragile X syndrome

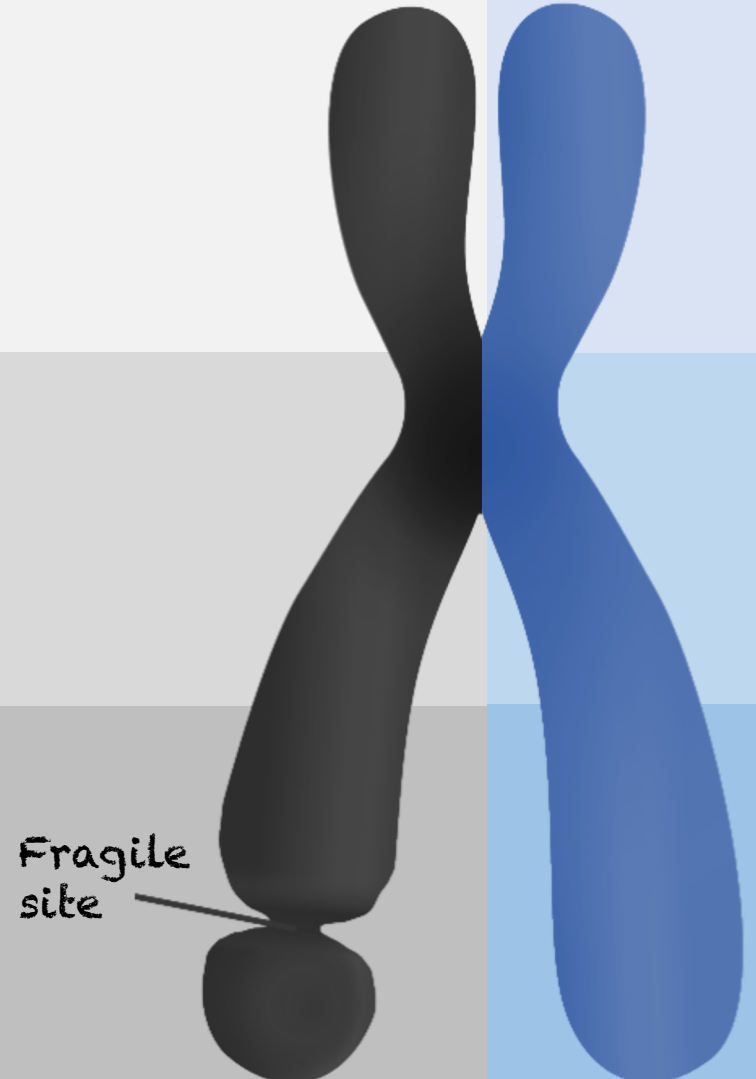
Intellectual disabilities

Physical anomalies

Behavioural characteristics

35% Autism Spectrum Disorder

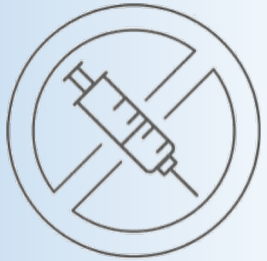




FMRP: Fragile X Messenger Ribonucleoprotein 1

NO treatment

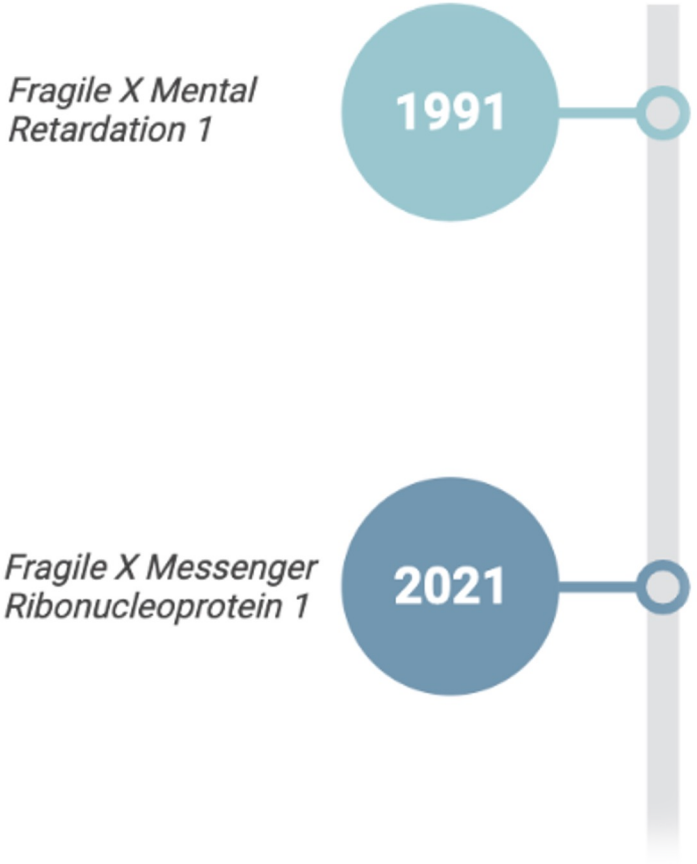
Educational therapies



A **mutation** in the ***FMR-1*** **gene** yielding the **absence of FMRP protein**

The optimal intervention would be to **restore the function of the FMRP protein.**

The history of FMRP protein, a Multifunctional RNA-binding Protein



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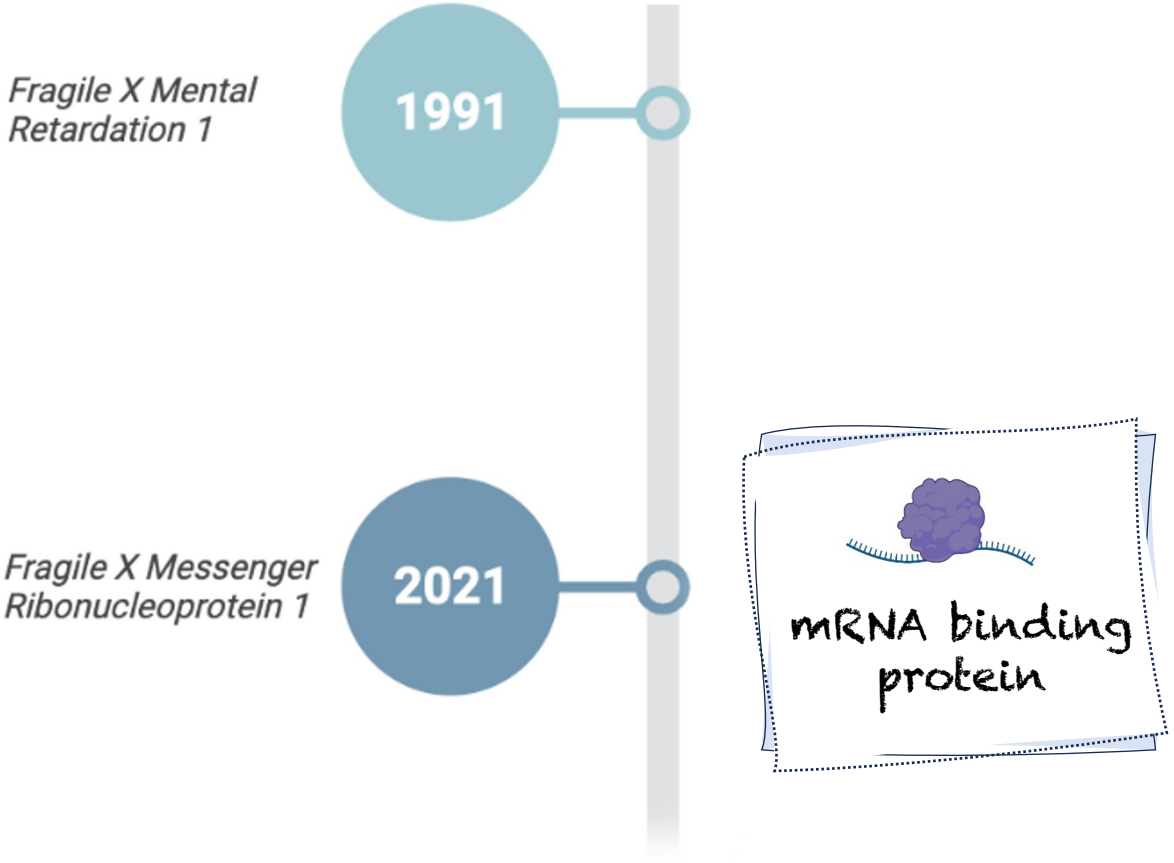
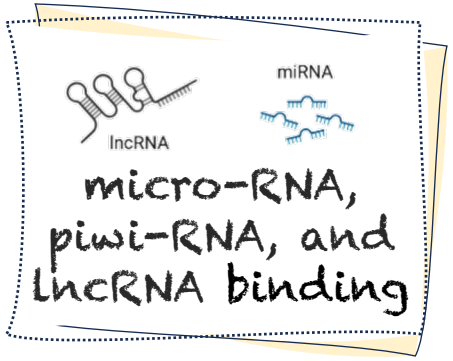


The history of FMRP protein, a Multifunctional RNA-binding Protein

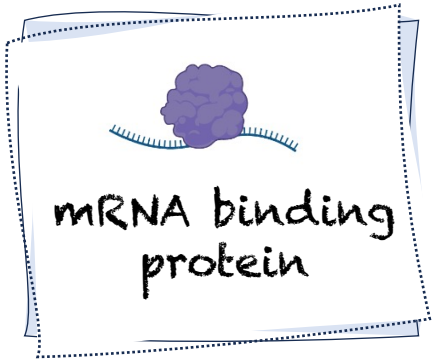
Fragile X Mental Retardation 1

1991



Fragile X Messenger Ribonucleoprotein 1

2021



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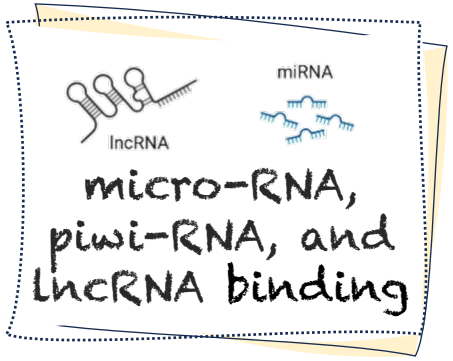

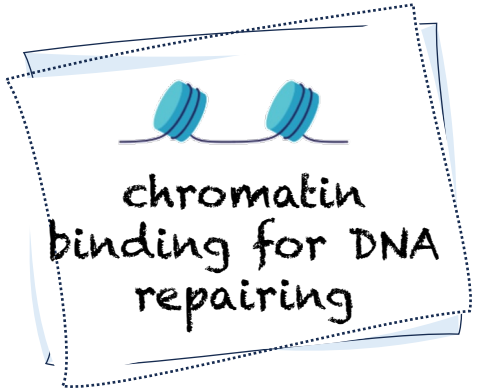

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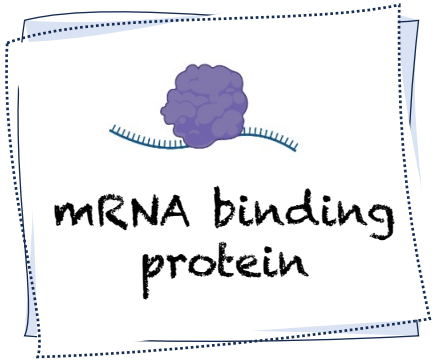

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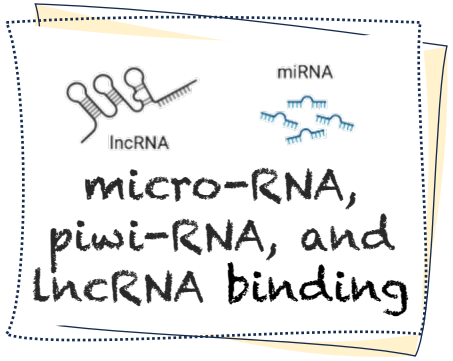

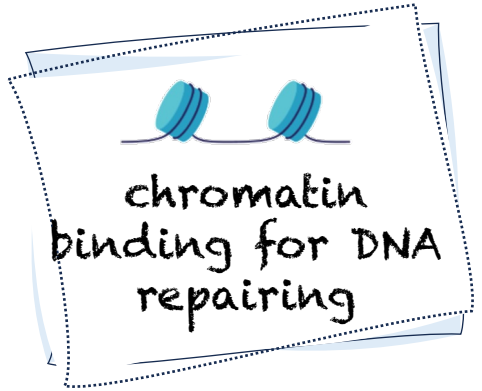

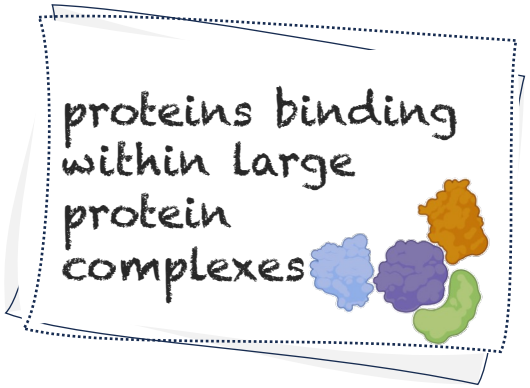

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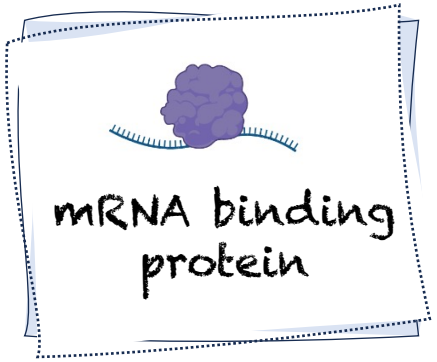

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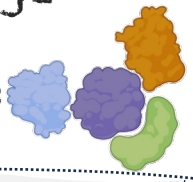
micro-RNA, piwi-RNA, and lncRNA binding

chromatin binding for DNA repairing

proteins binding within large protein complexes



Fragile X Messenger Ribonucleoprotein 1

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mRNA binding protein

critical component of neuronal granules

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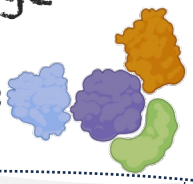

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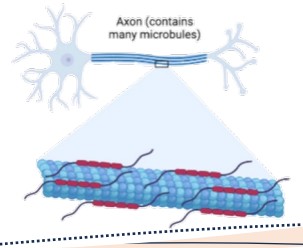
mRNA binding protein

critical component of neuronal granules

bridge between these granules and microtubule elements



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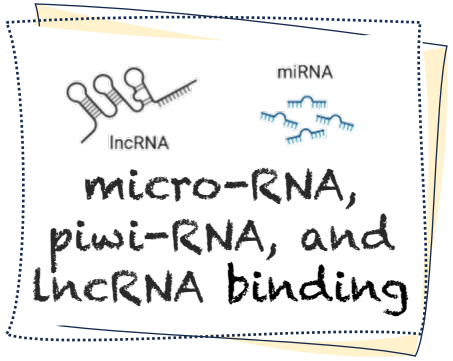

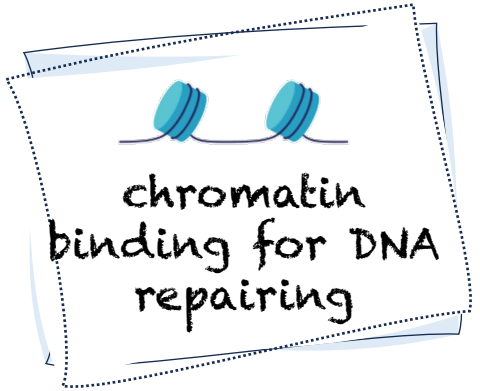

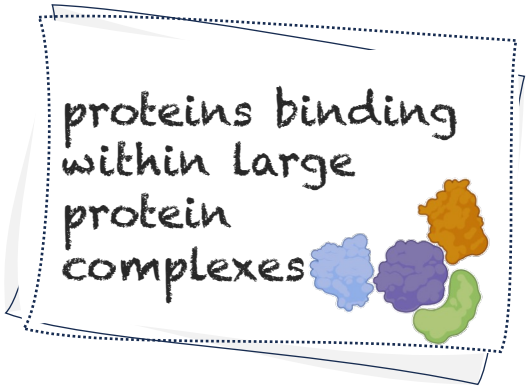

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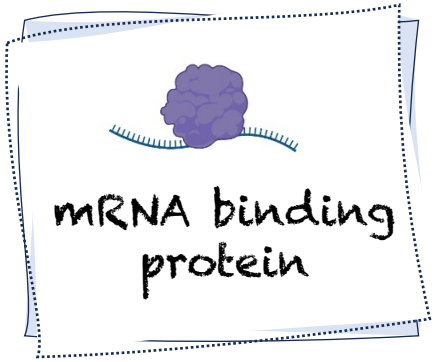
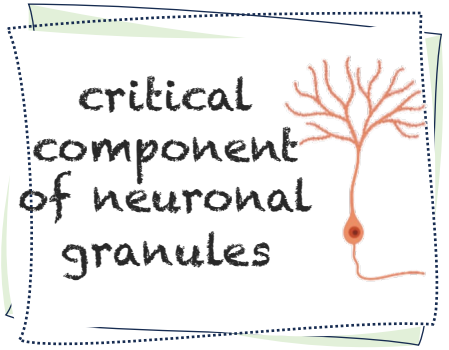


More than 30 functional categories



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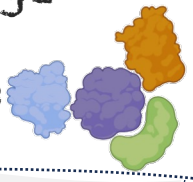

Fragile X Messenger Ribonucleoprotein 1

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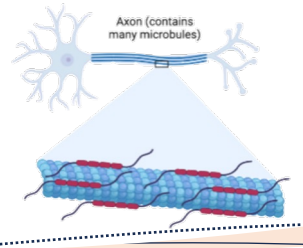
mRNA binding protein

More than 30 functional categories

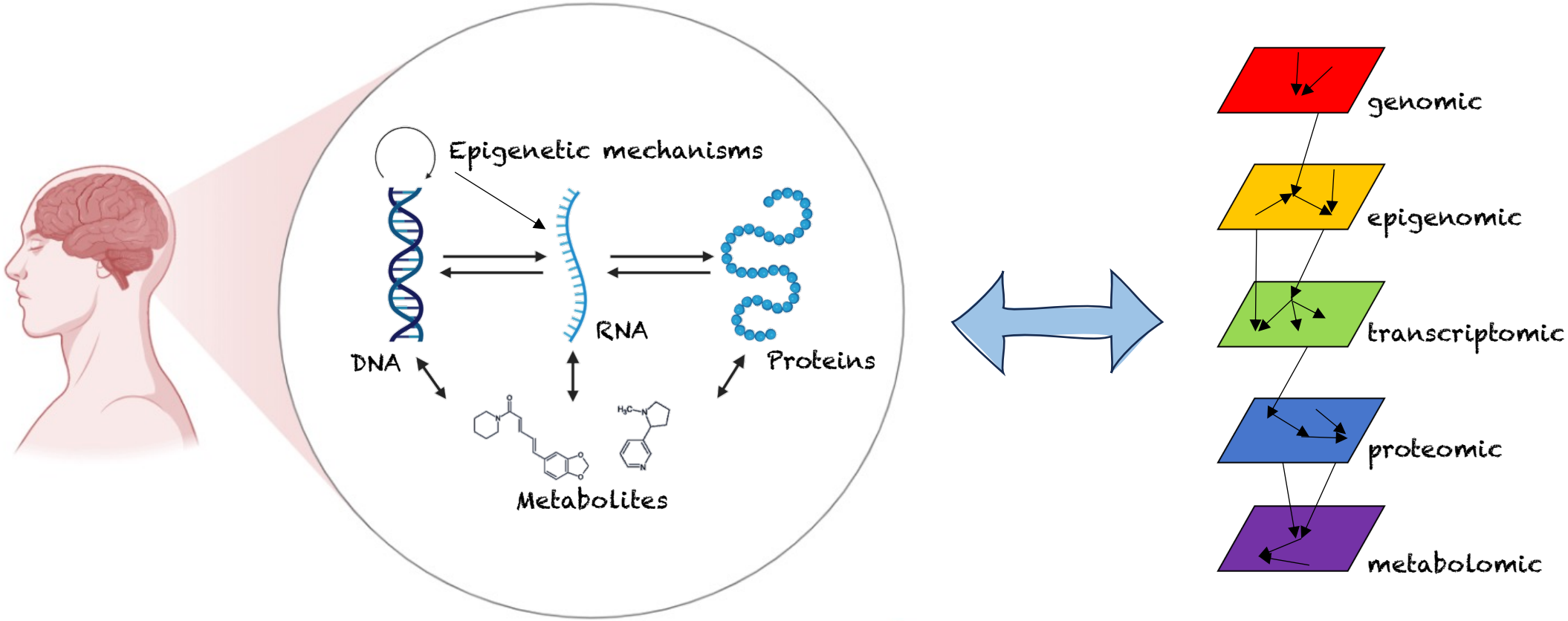
critical component of neuronal granules

Is that all?

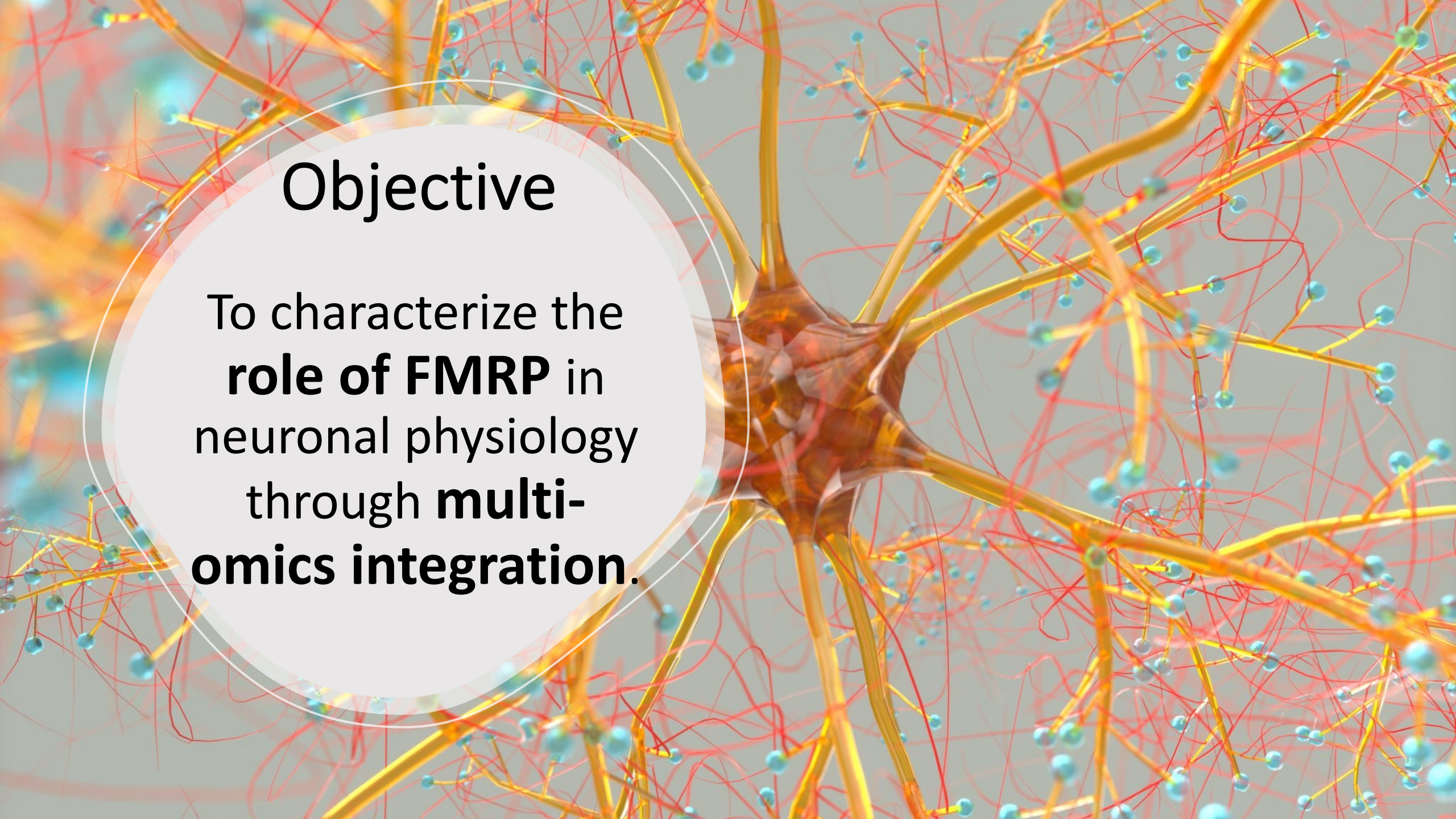
bridge between these granules and microtubule elements



How to characterize the multiple roles of FMRP?



Understanding the multiple roles of FMRP by using multi-omics integration.



Objective

To characterize the **role of FMRP** in neuronal physiology through **multi-omics integration**.

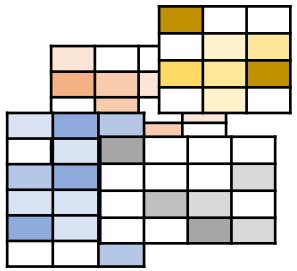
Data collection

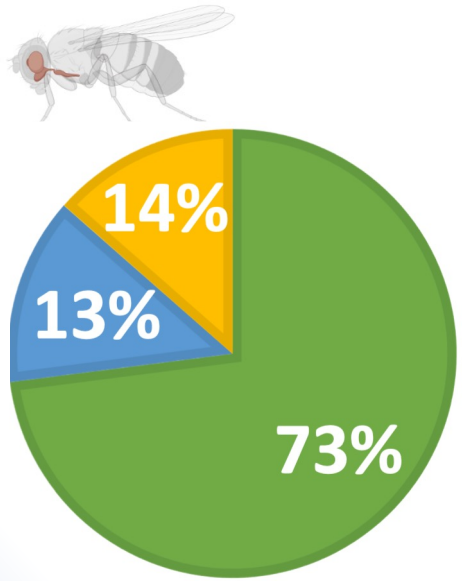
Experimental design

FMRP WT

FMRP KO

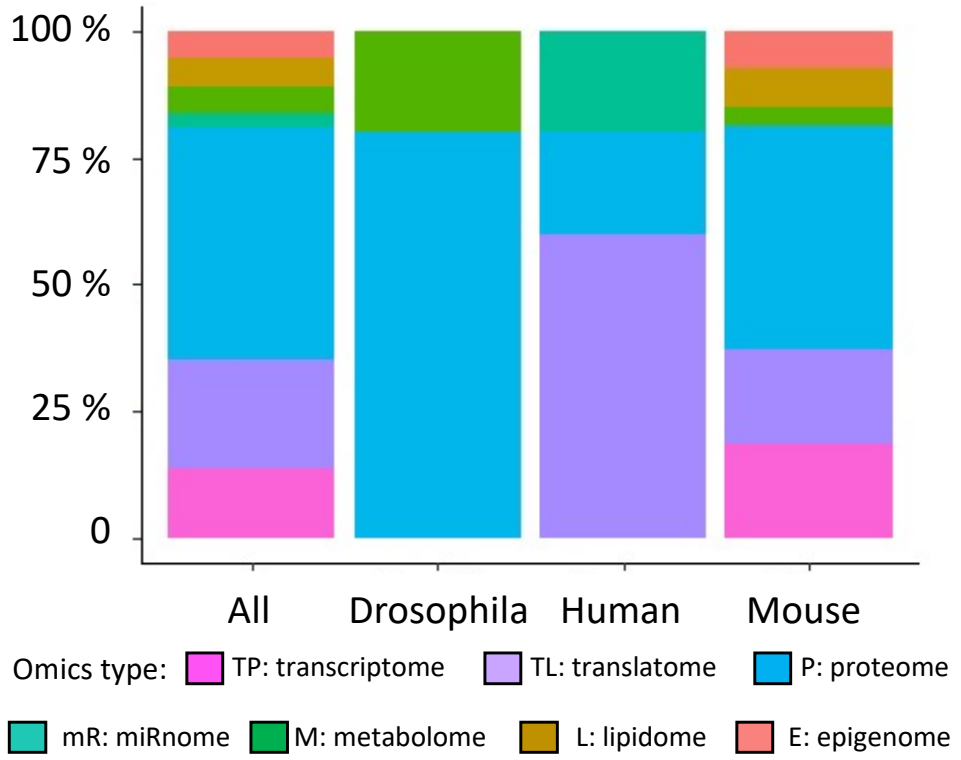
Public databases



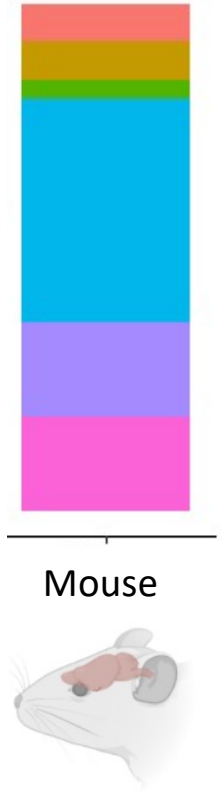


43 Multi-omics datasets

7 different type of omics



The pilot integrated dataset



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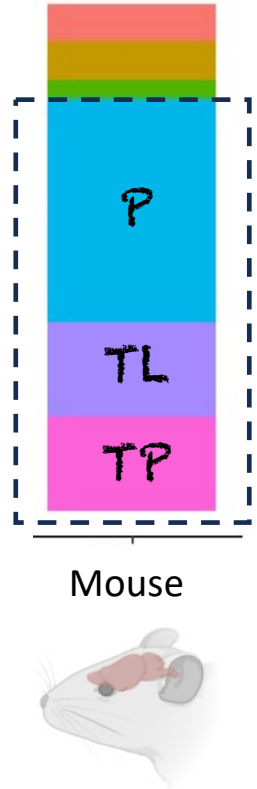

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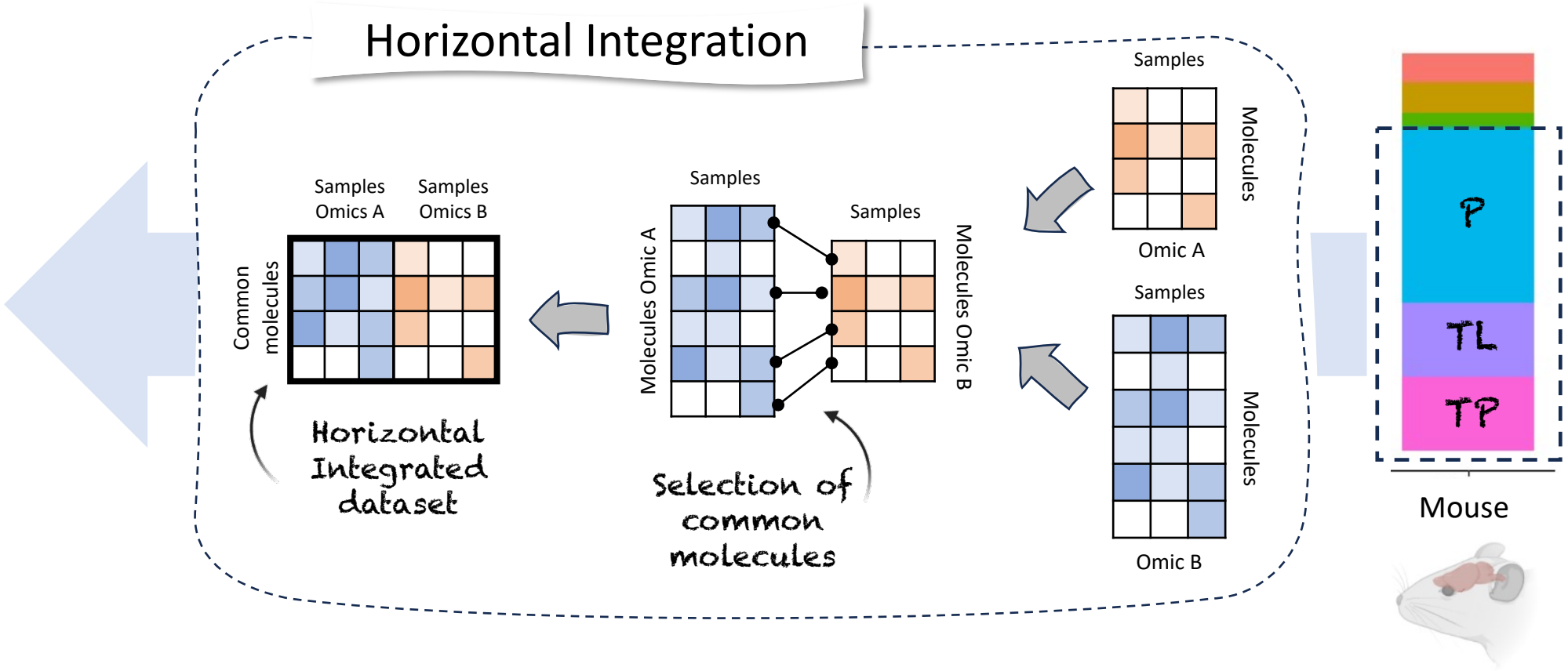

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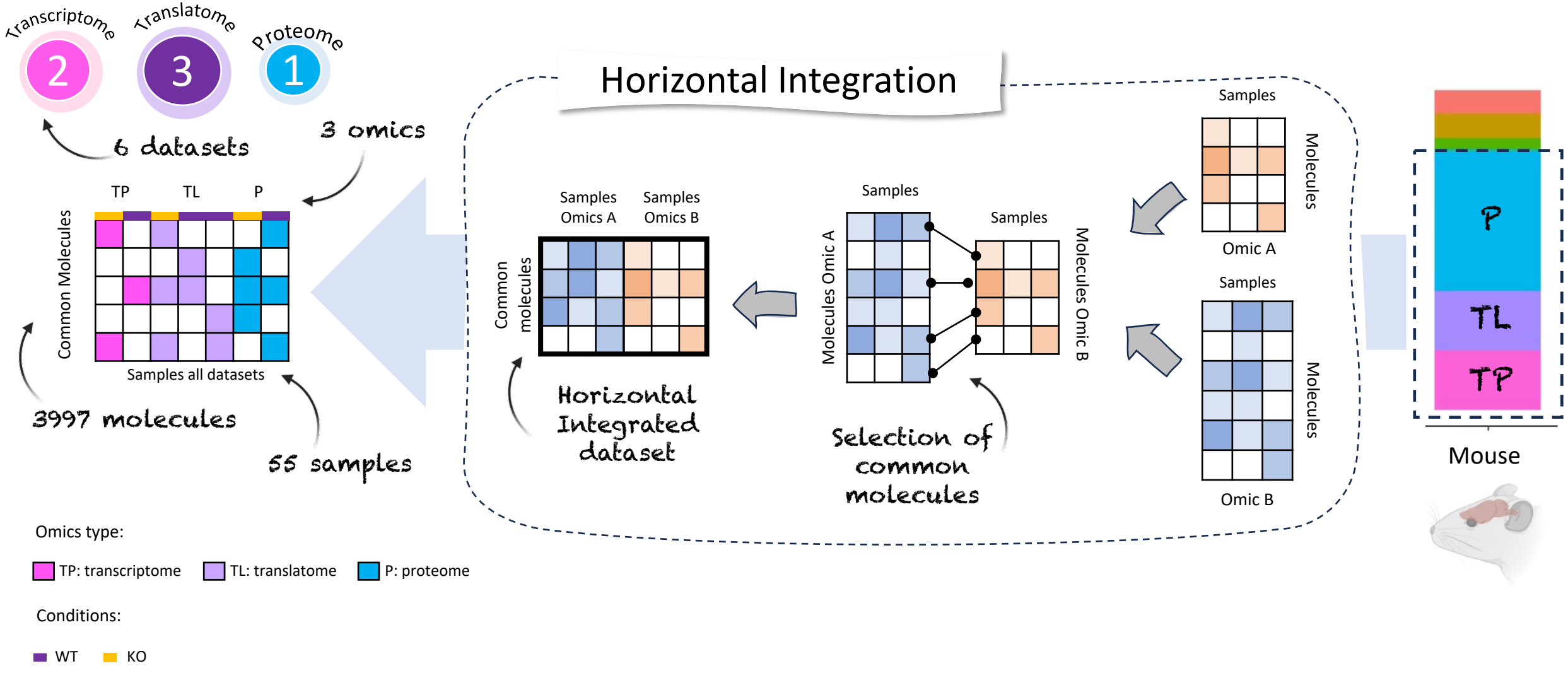
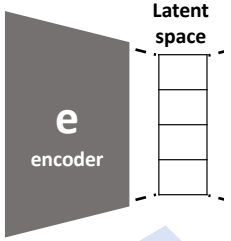


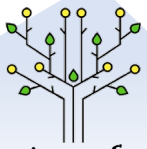
HIVE: a general framework to analyse integrated multi-omics data

Secret code
=
Multi-omics data

HIVE

Variational Autoencoder



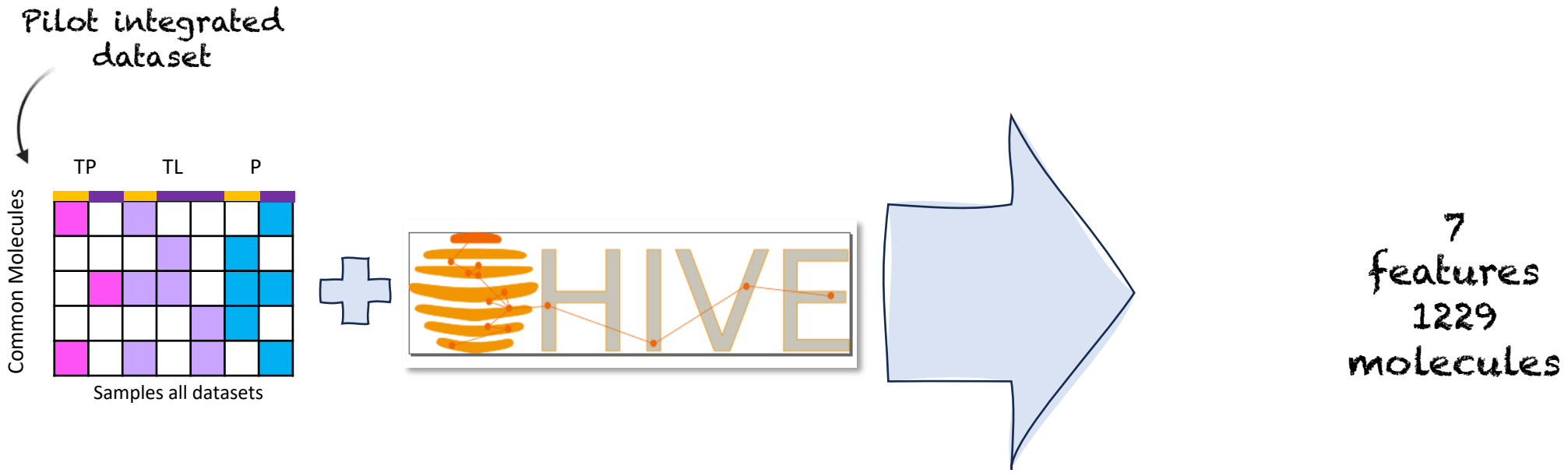


Random forest regression

Molecules contribution to each latent feature
=
The key to convert the secret code

Decrypted code
=
Latent features

Application of HIVE on the pilot integrated dataset



Each feature identifies a specific set of molecules that might correspond to different biological meanings.

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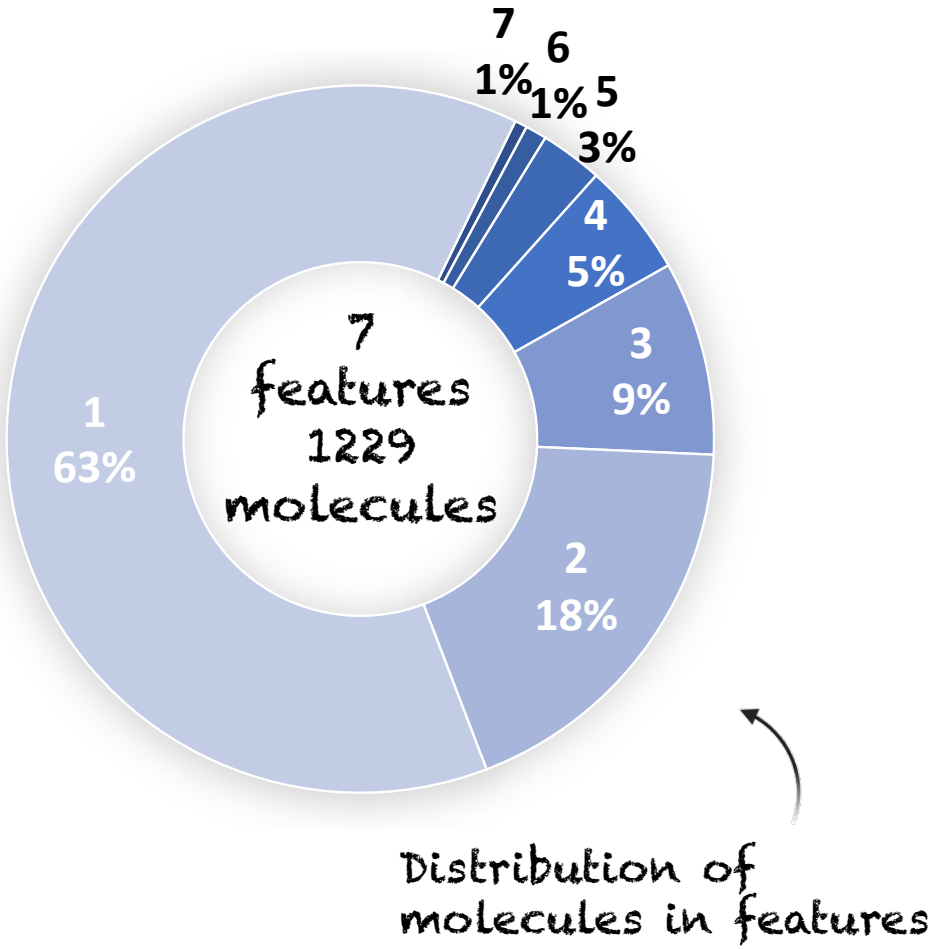

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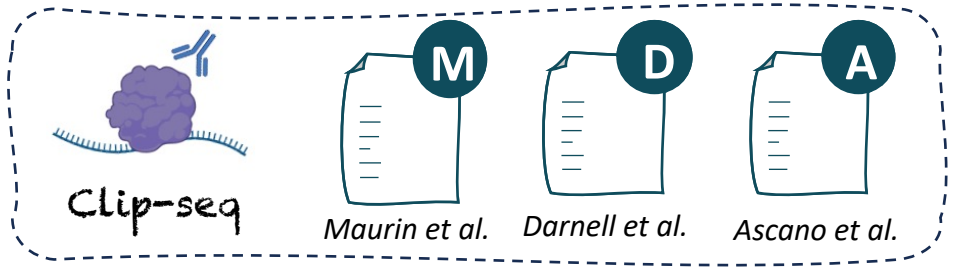
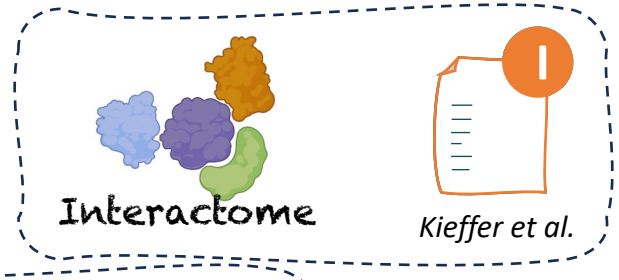
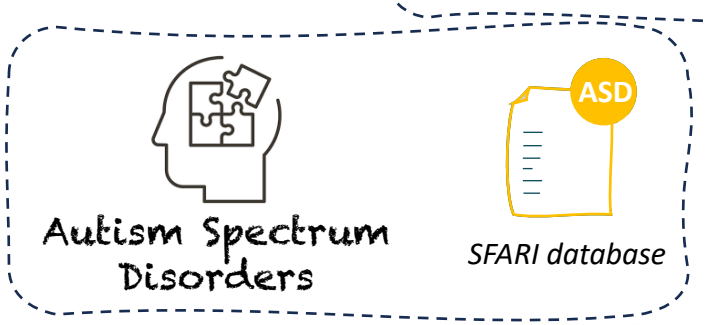
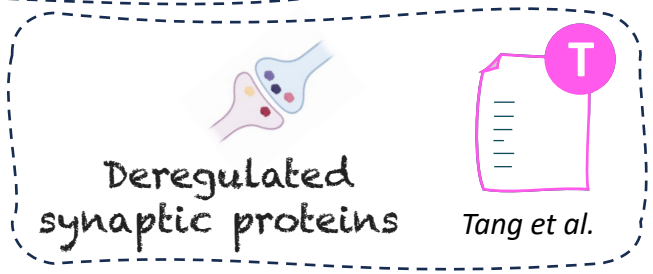
Characterization of the molecules found by HIVE









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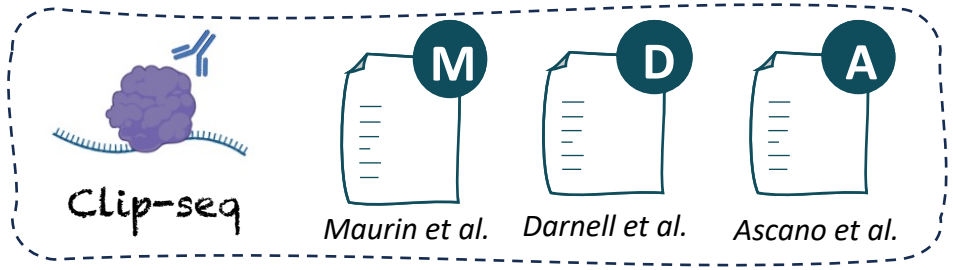

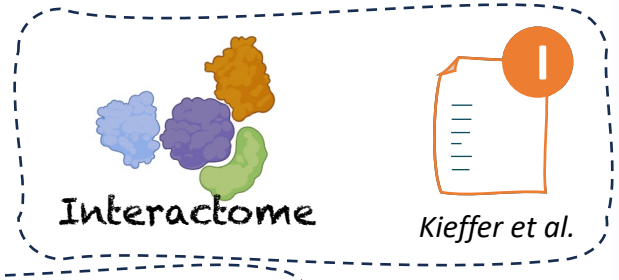

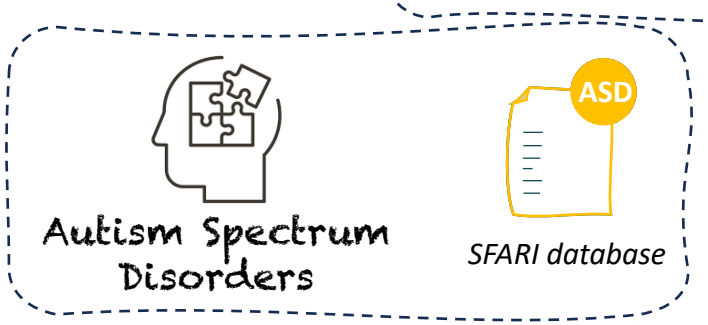

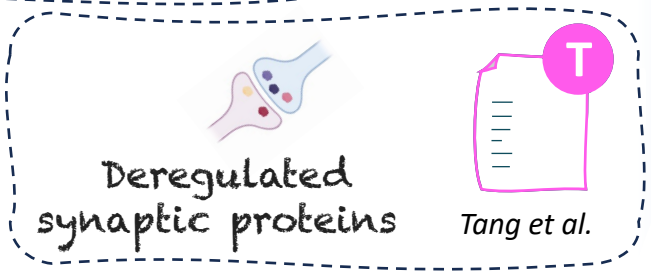

1229 molecules

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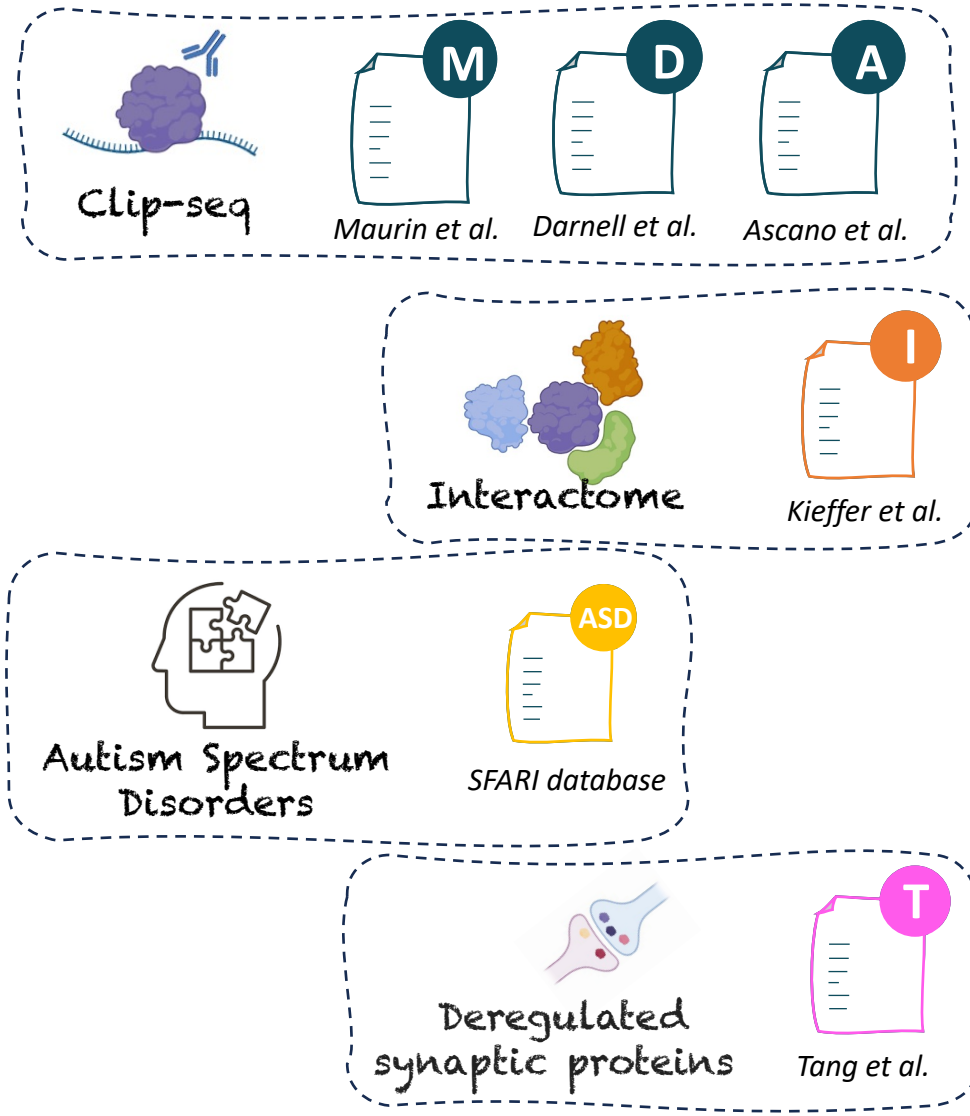
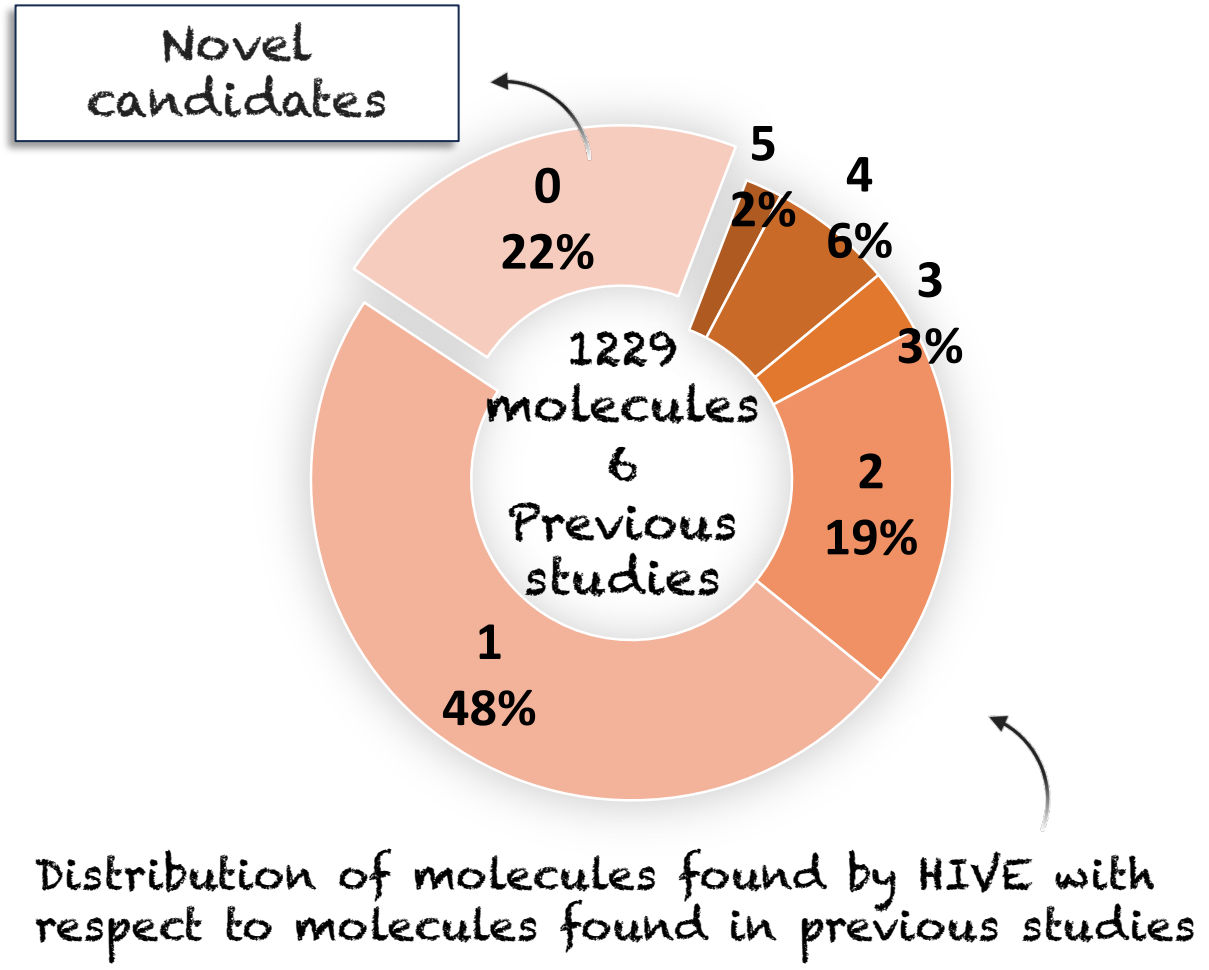
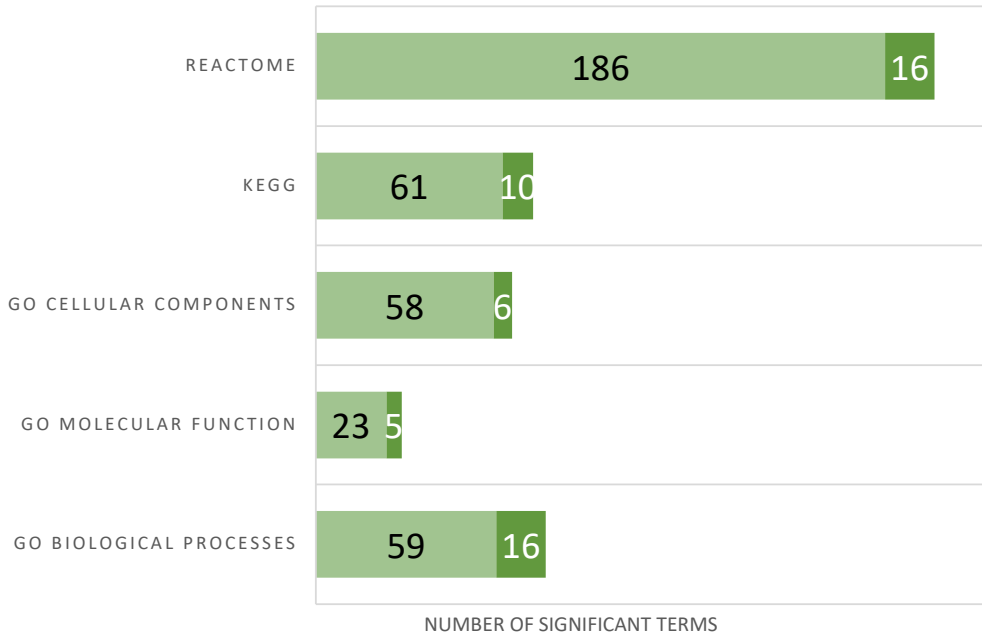




Distribution of molecules found by HIVE with respect to molecules found in previous studies

Global characterization of functional processes



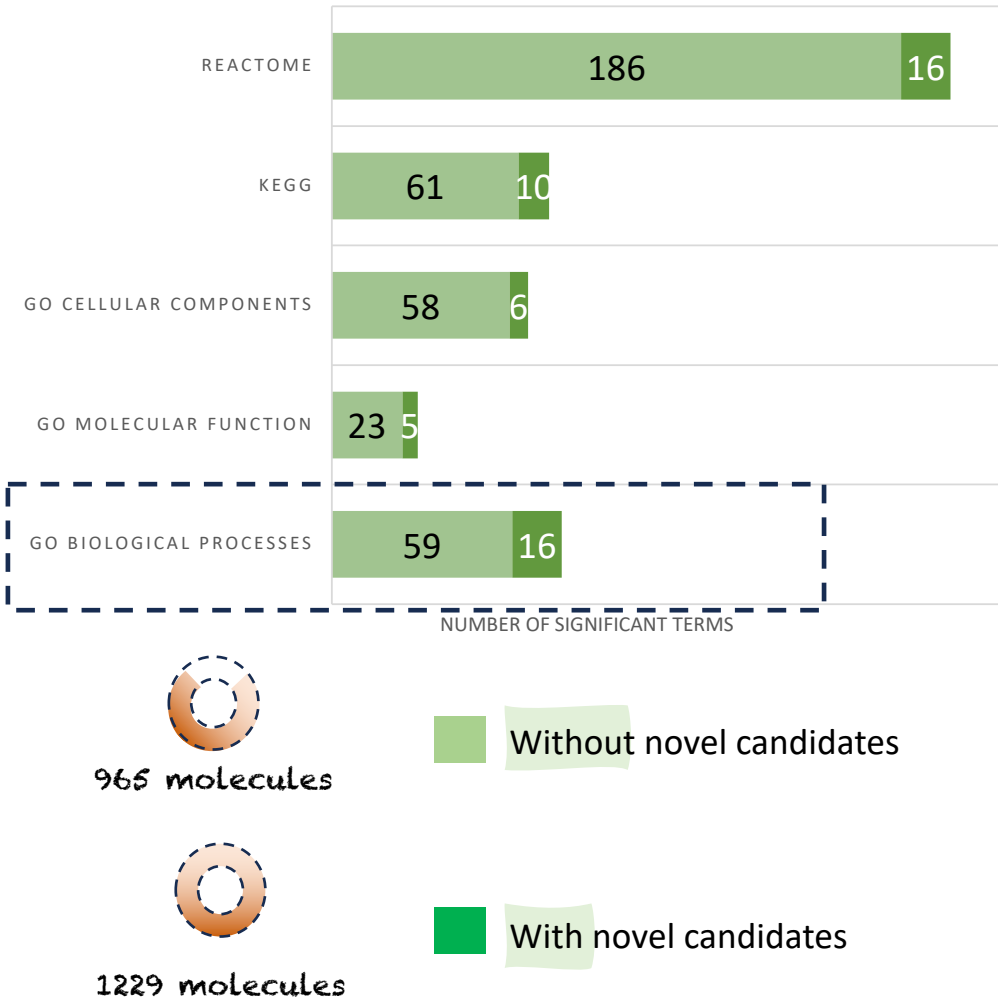
965 molecules

Without novel candidates

1229 molecules

With novel candidates

Global characterization of functional processes



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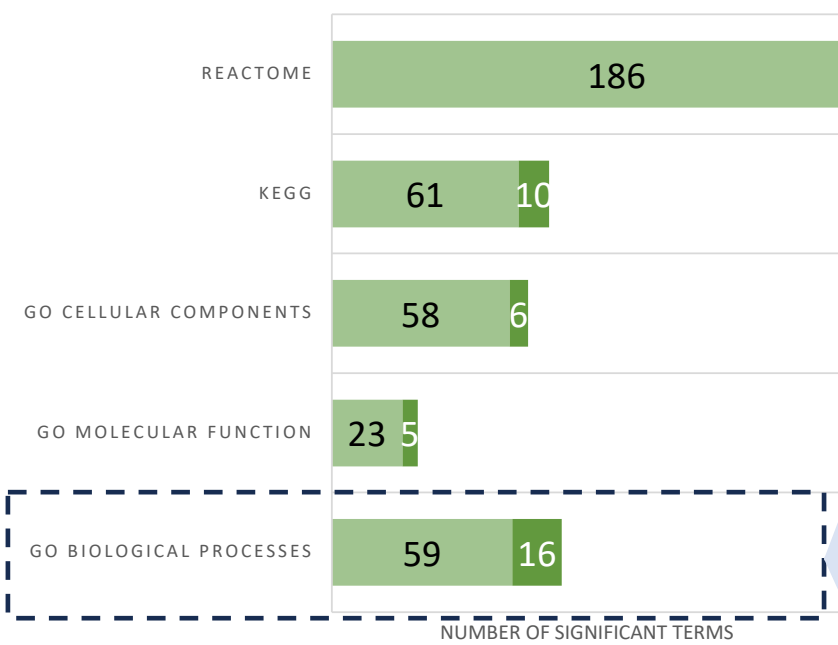


965 molecules

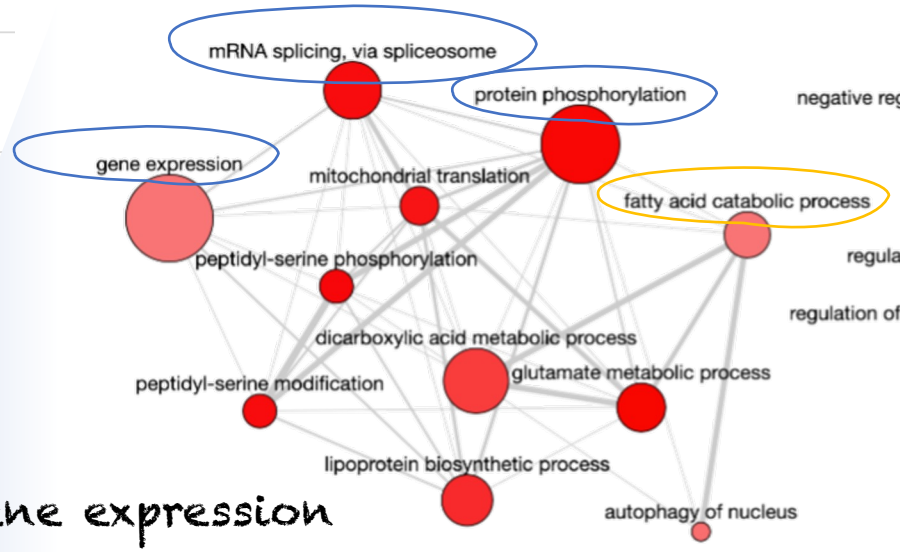
Without novel candidates

1229 molecules

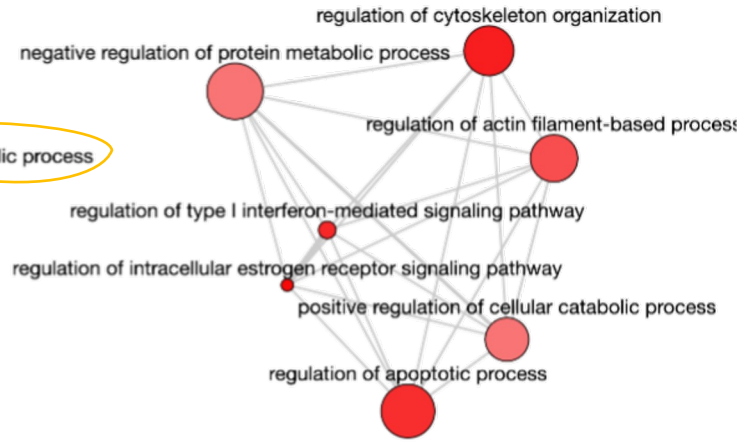
With novel candidates

Known term

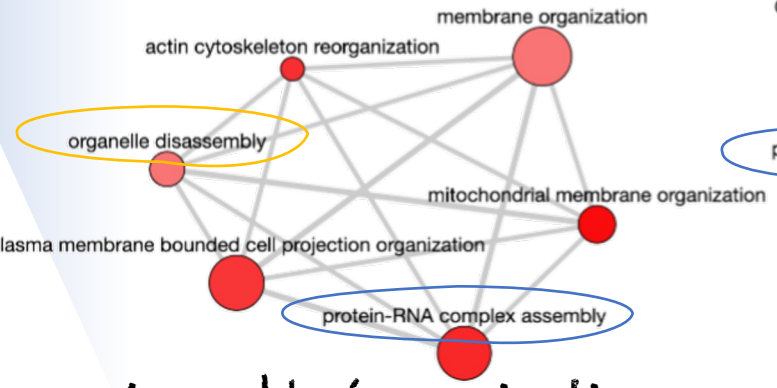
Term found with novel candidtes



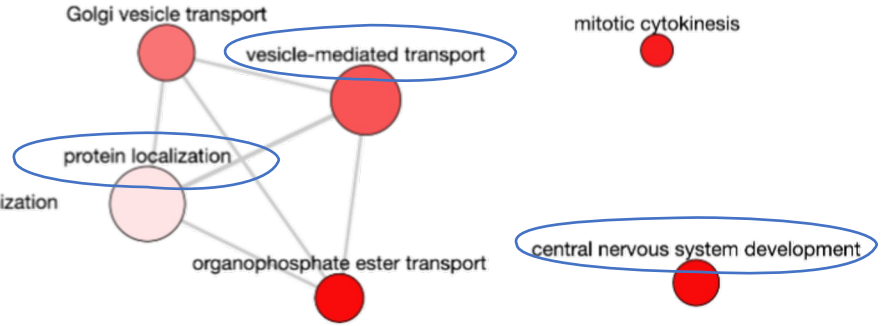
Gene expression



Regulatory mechanisms

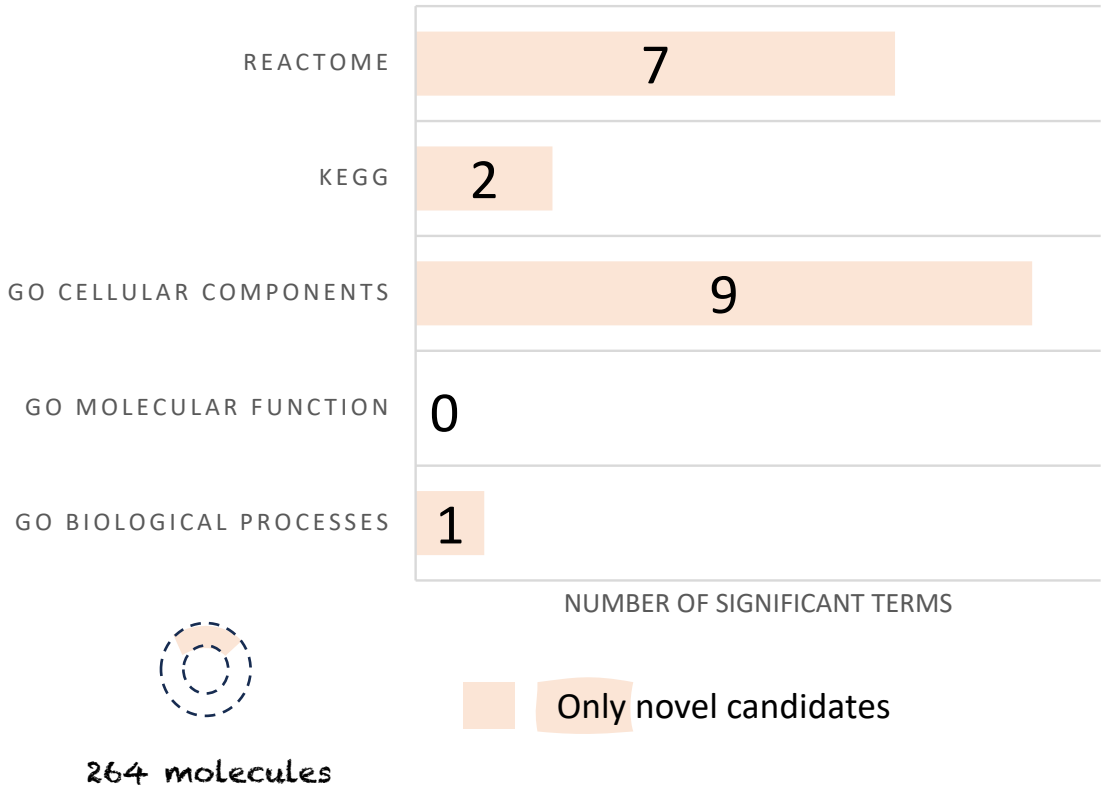


Assembly/organization



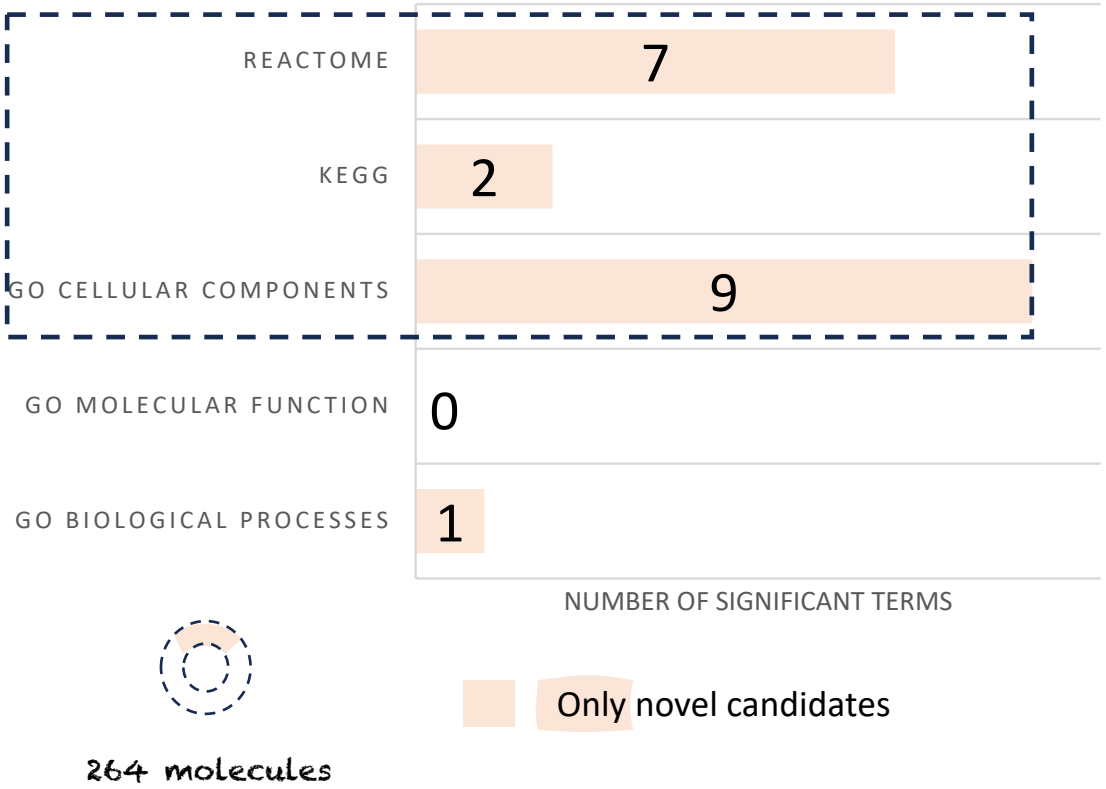
Transport

Global characterization of functional processes

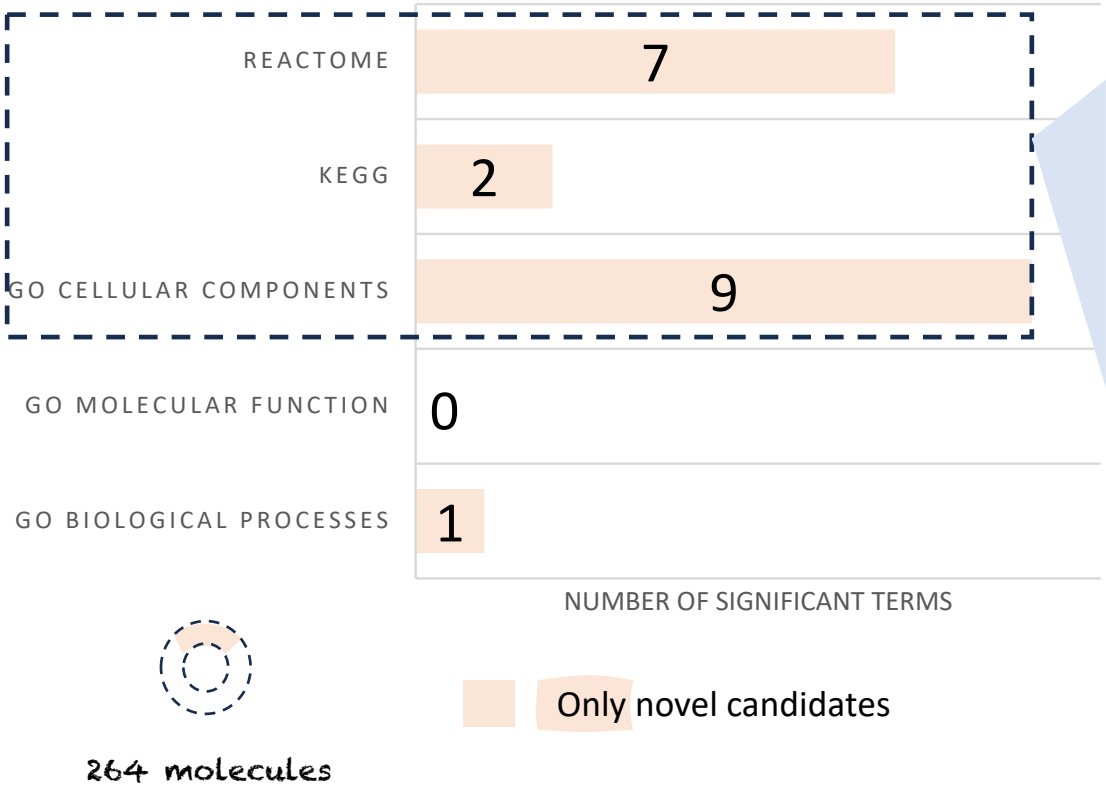


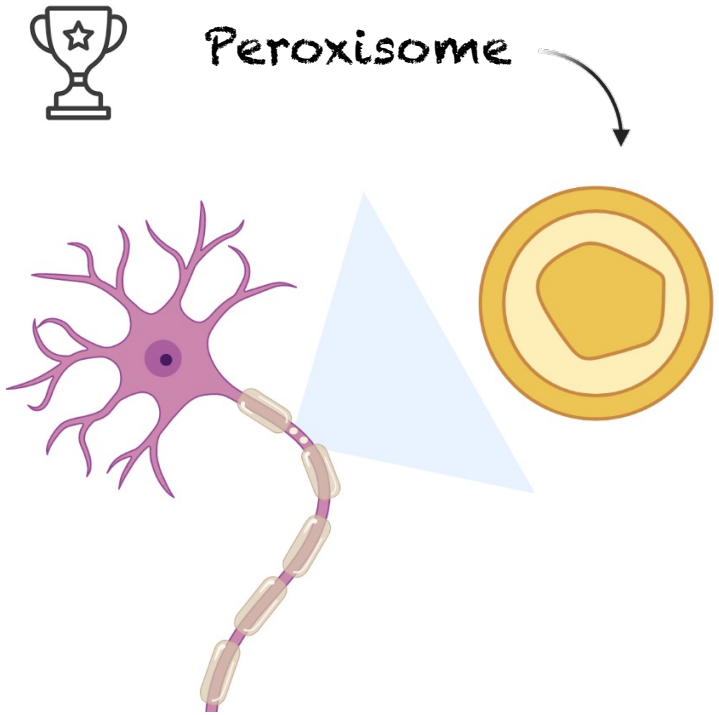
264 molecules

Global characterization of functional processes



Global characterization of functional processes





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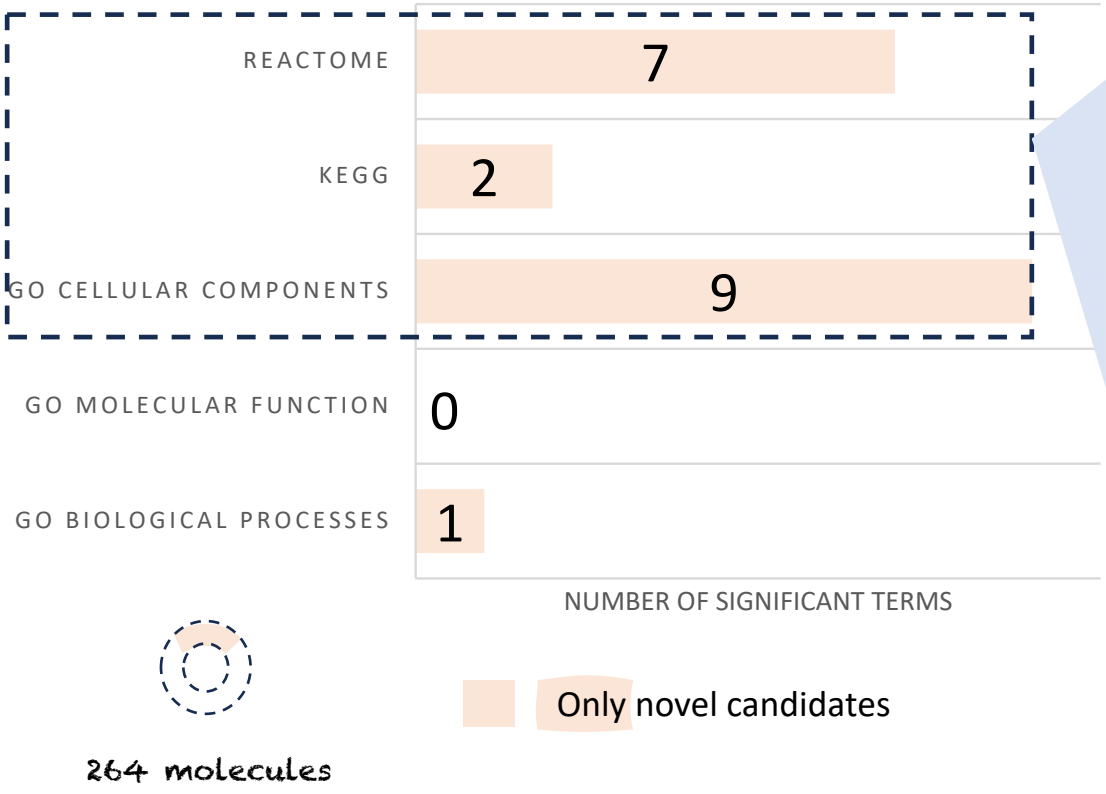
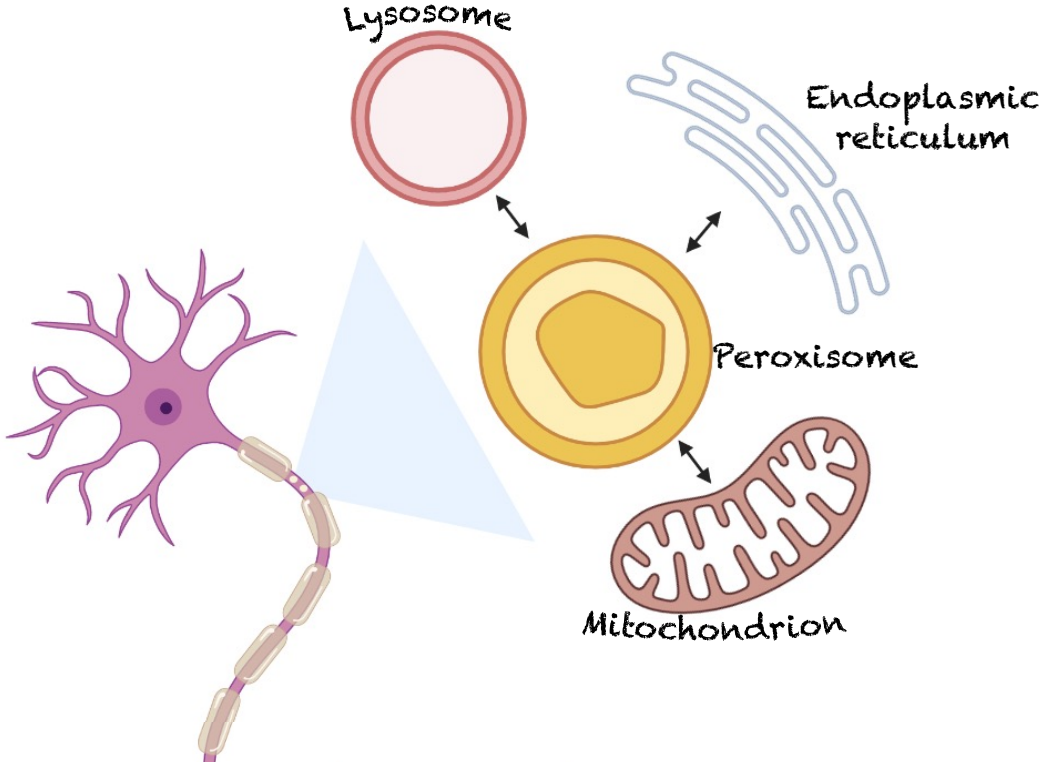
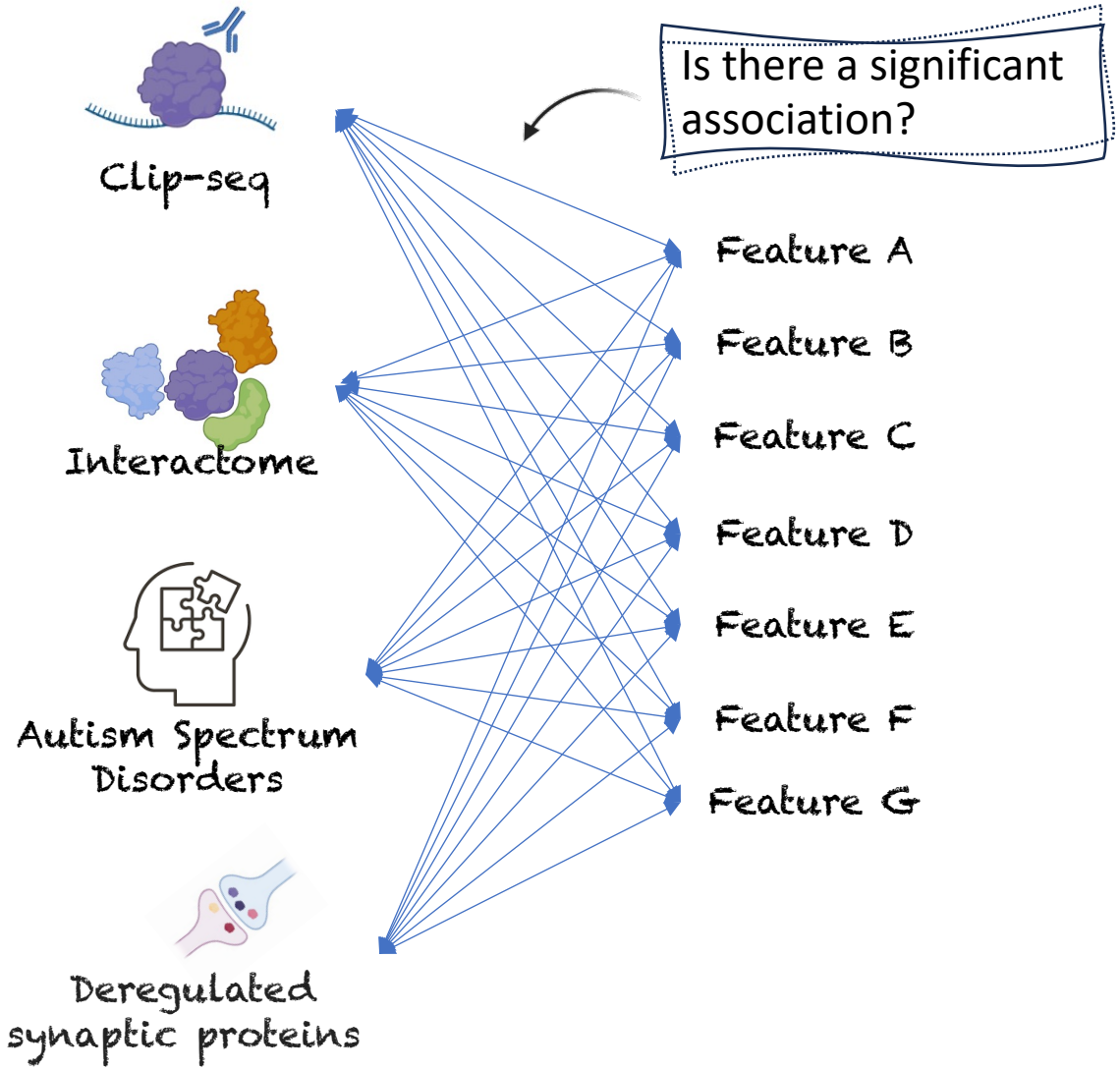




Peroxisomes play critical roles in maintaining cellular health, especially in the central nervous system.

Characterization of the features found by HIVE



Characterization of the features found by HIVE

Clip-seq

Interactome

Autism Spectrum Disorders

Deregulated synaptic proteins

Is there a significant association?

Feature A

Feature B

Feature C

Feature D

Feature E

Feature F

Feature G

Market basket analysis

Significant associations between items that are often bought together.

Characterization of the features found by HIVE

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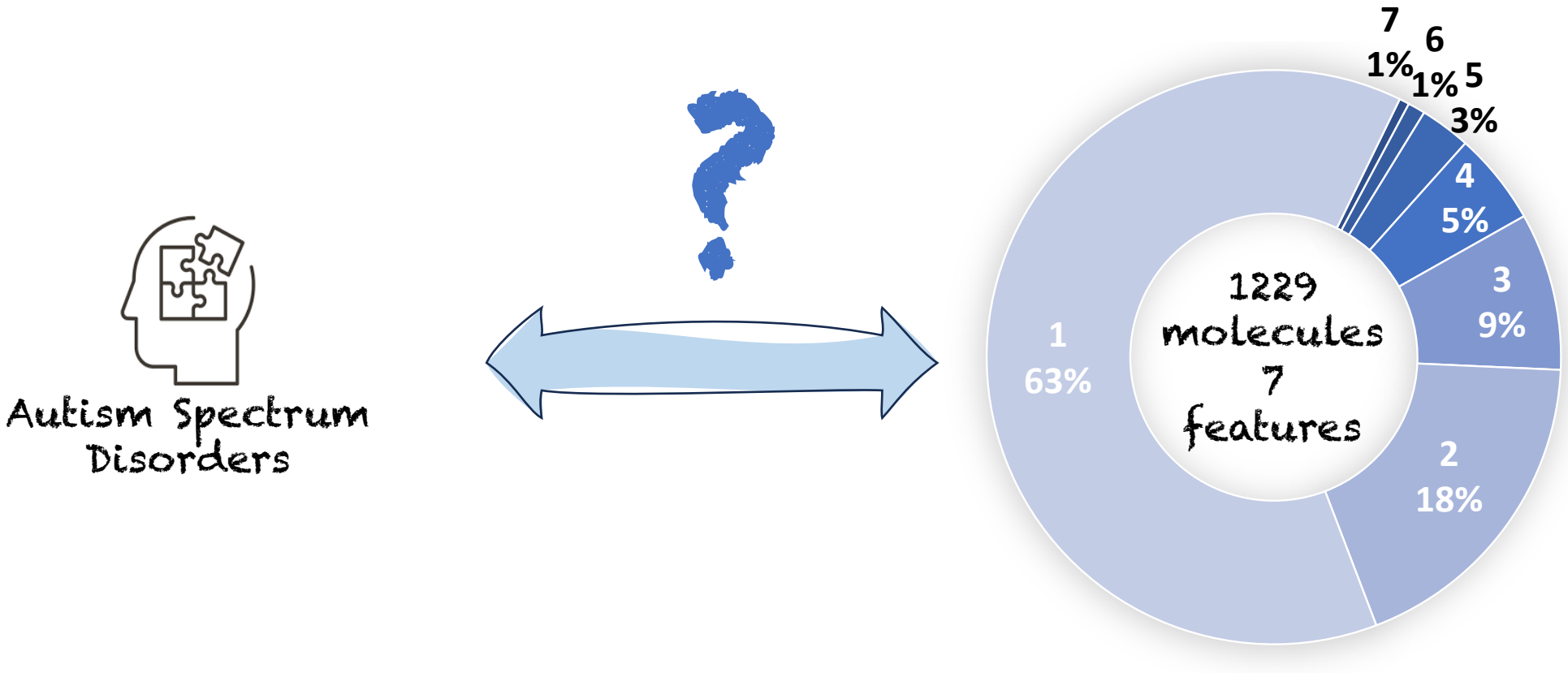
Market basket analysis

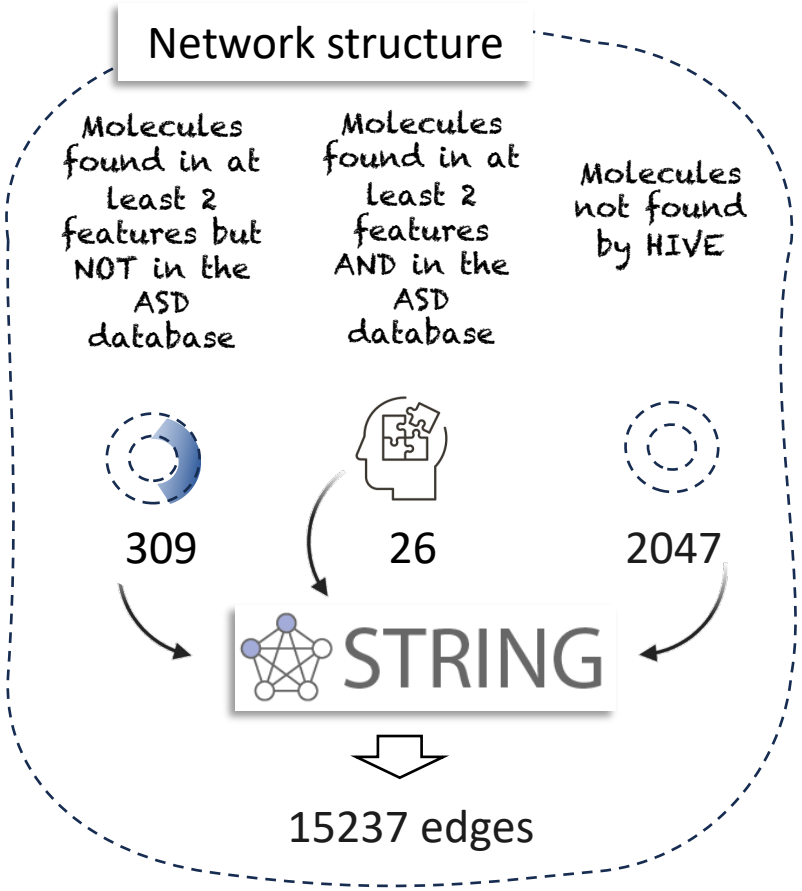
Significant associations between items that are often bought together.

Features encoded in the latent space capture specific biological processes linked to the phenotype under study.

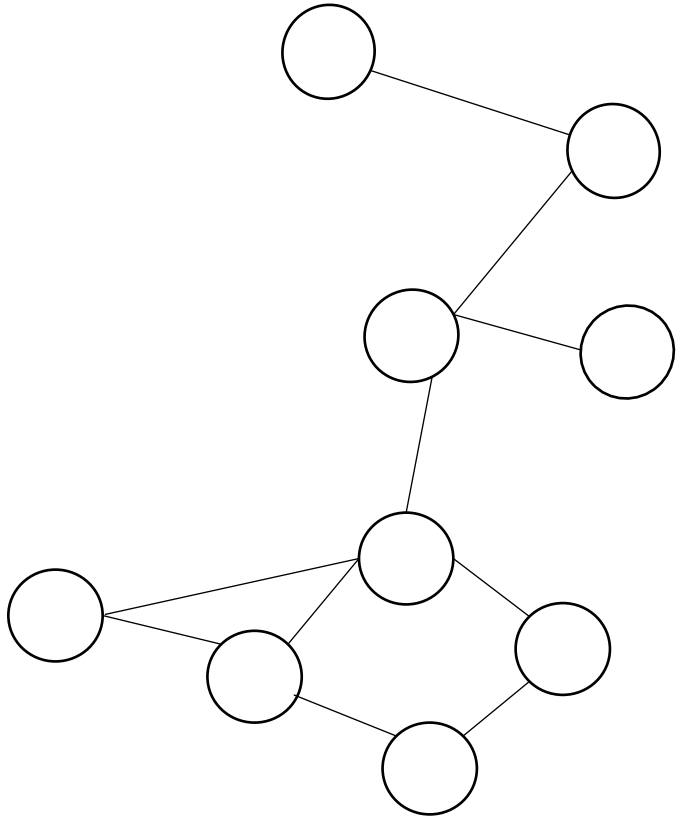
Can we identify novel putative candidate molecules that link ASD and FMRP?

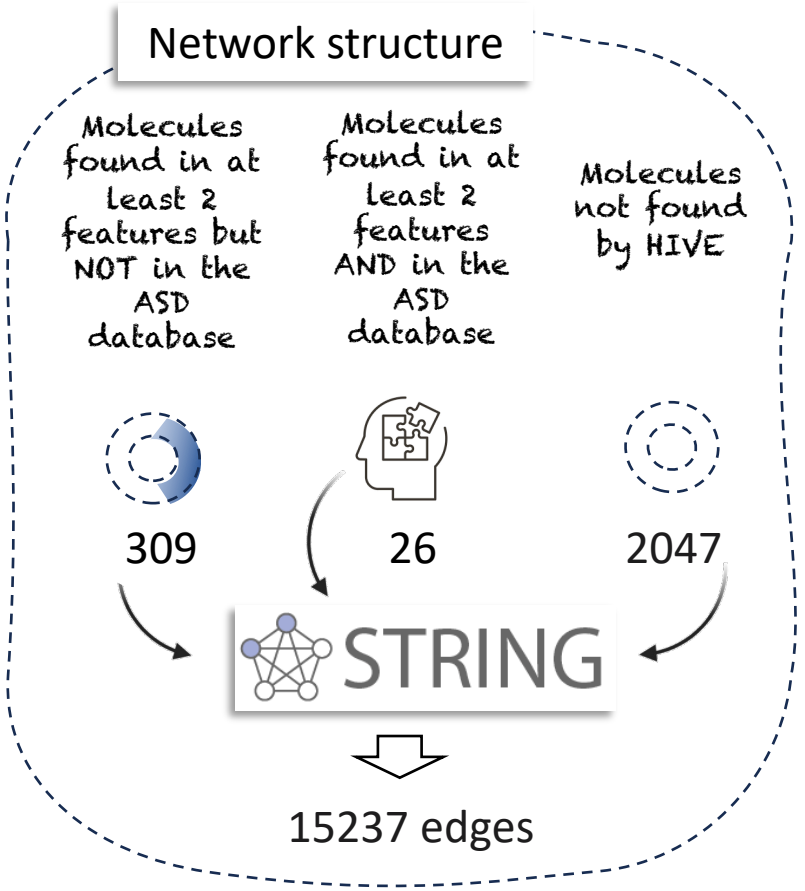


Strategy


Network structure
Molecules found in at least 2 features but NOT in the ASD database
Molecules found in at least 2 features AND in the ASD database
Molecules not found by HIVE
309
26
2047
STRING
15237 edges

Strategy

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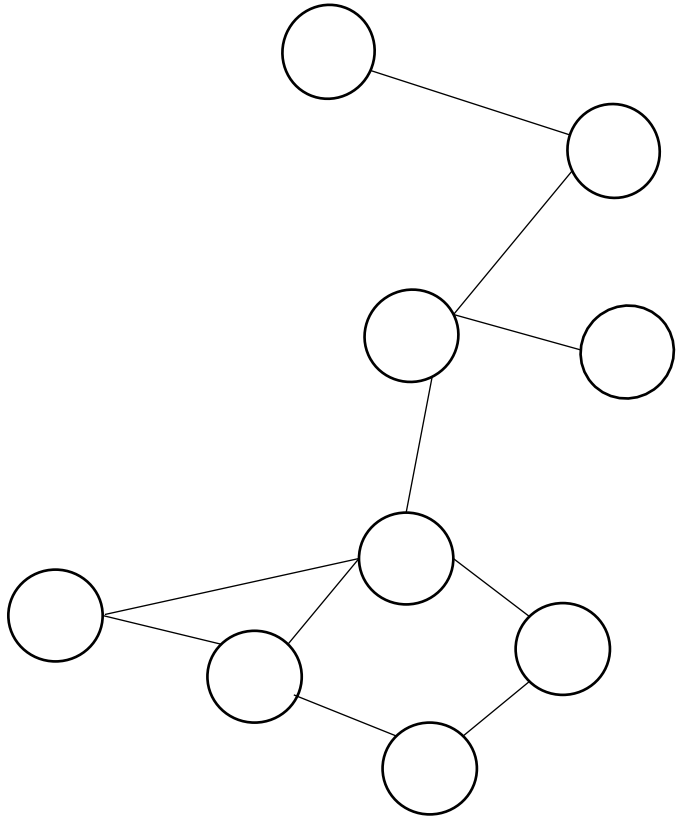

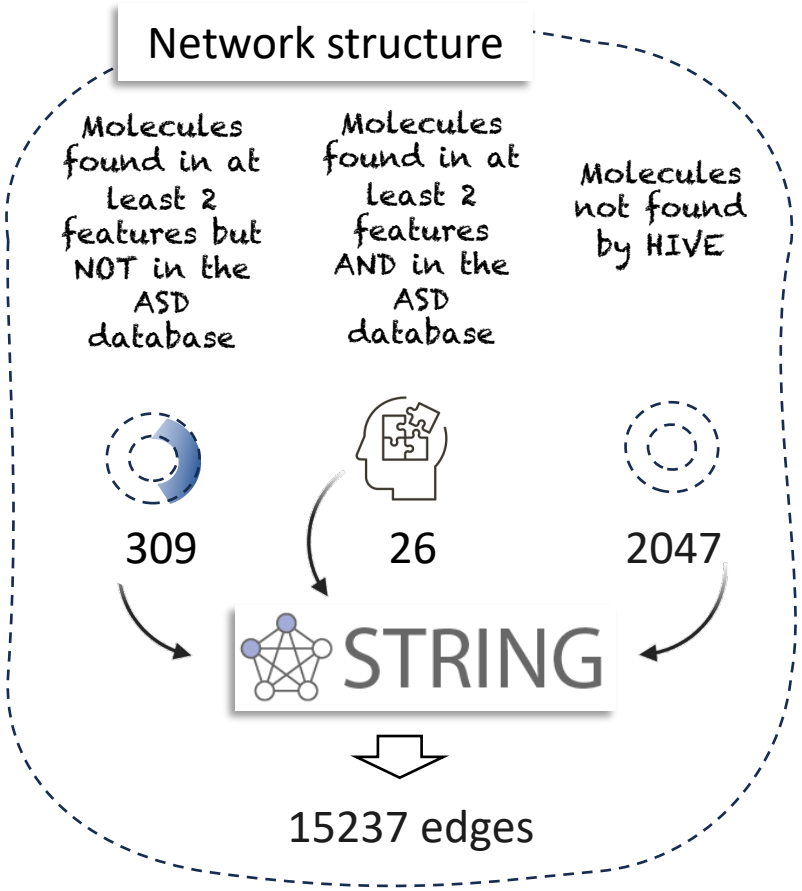
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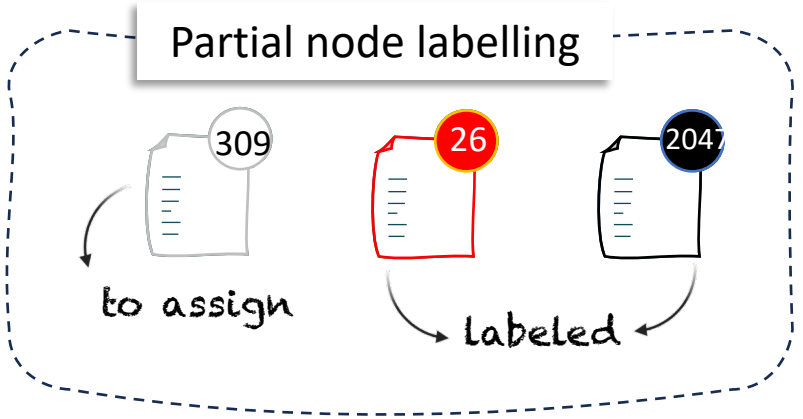
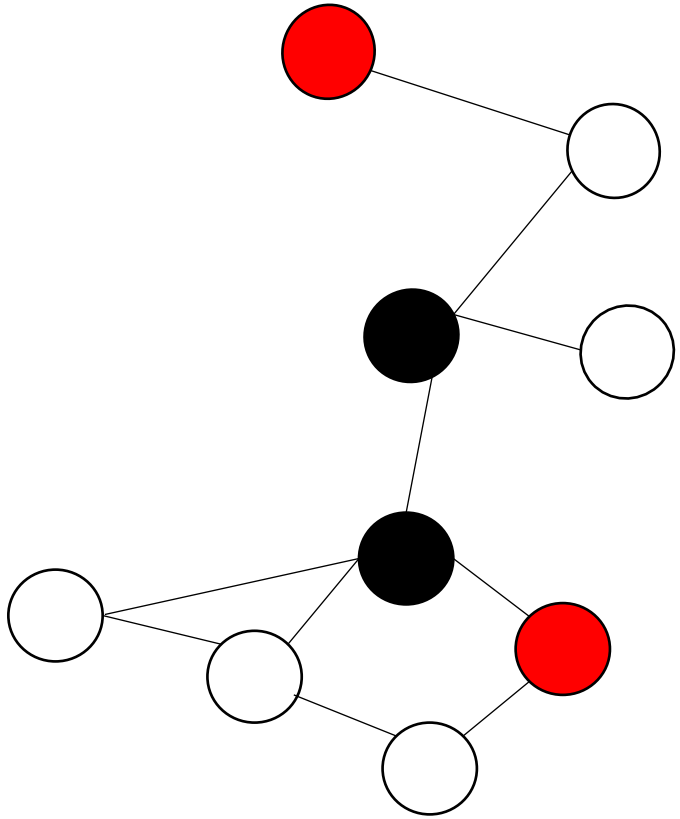
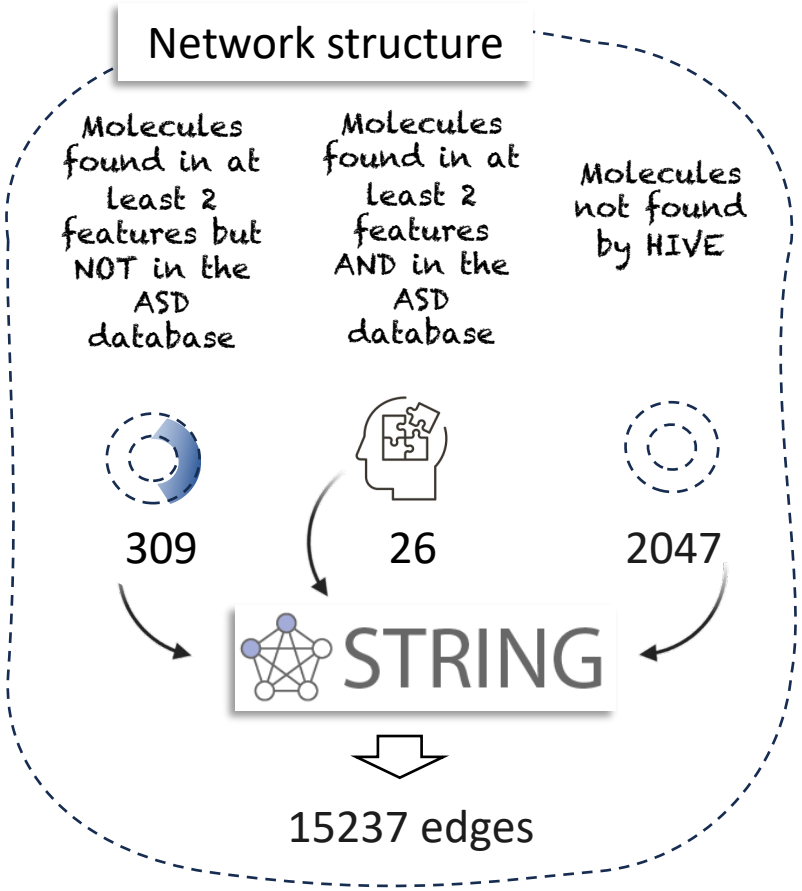

Partial node labelling
309
26
204
to assign
labeled

Strategy

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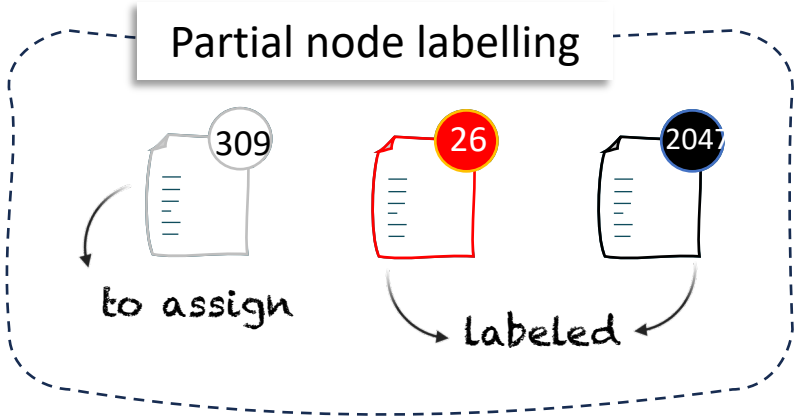
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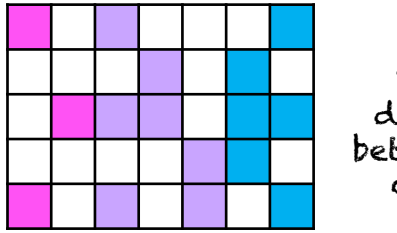
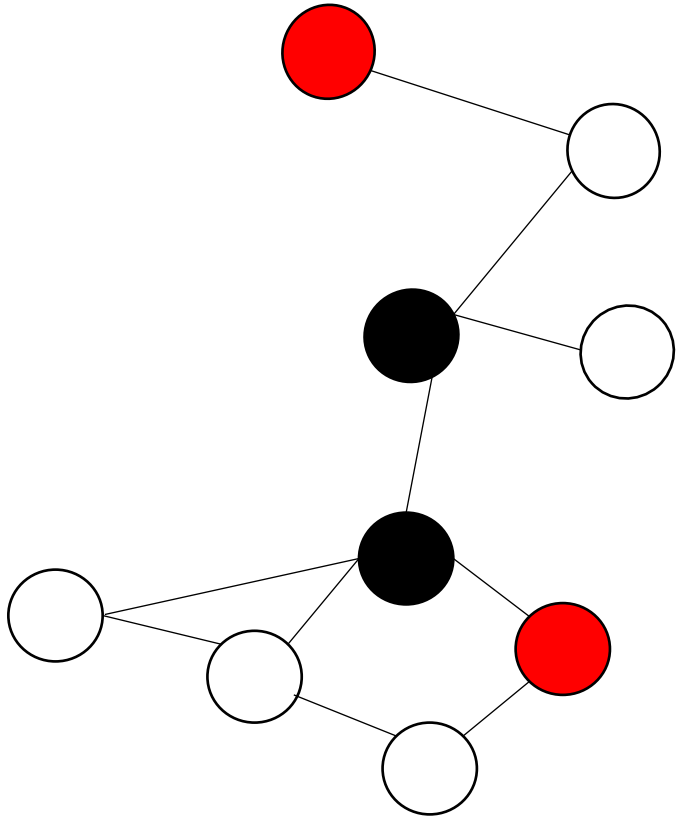
Strategy

Edge weights



Jensen-Shannon divergence between pairs of nodes

Multi-omics integrated dataset



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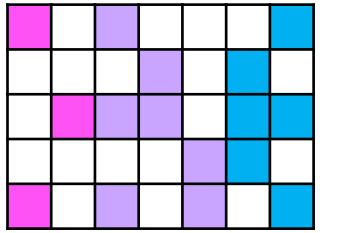

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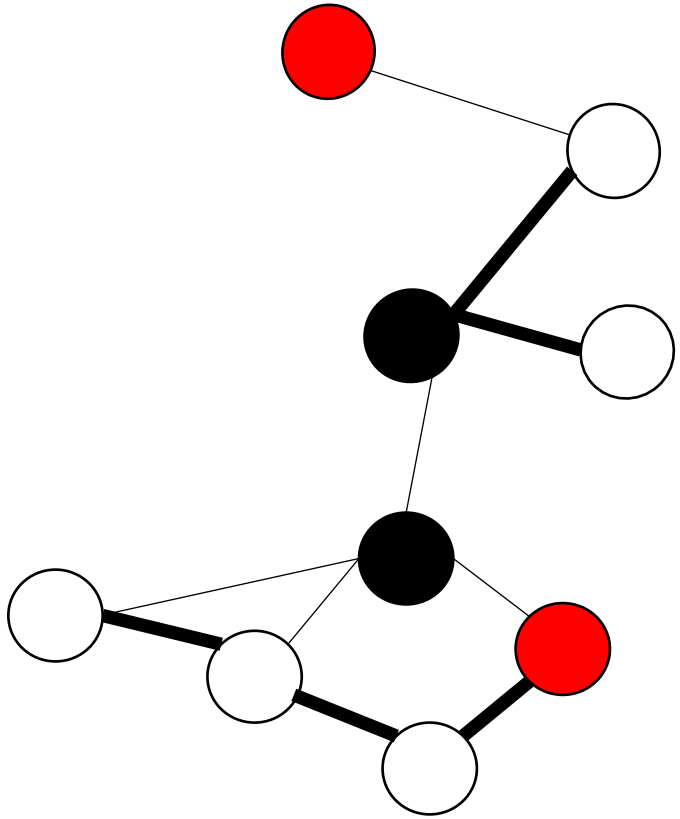

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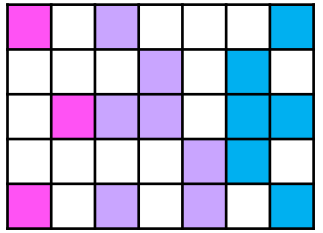

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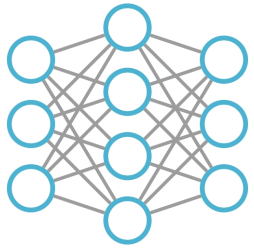
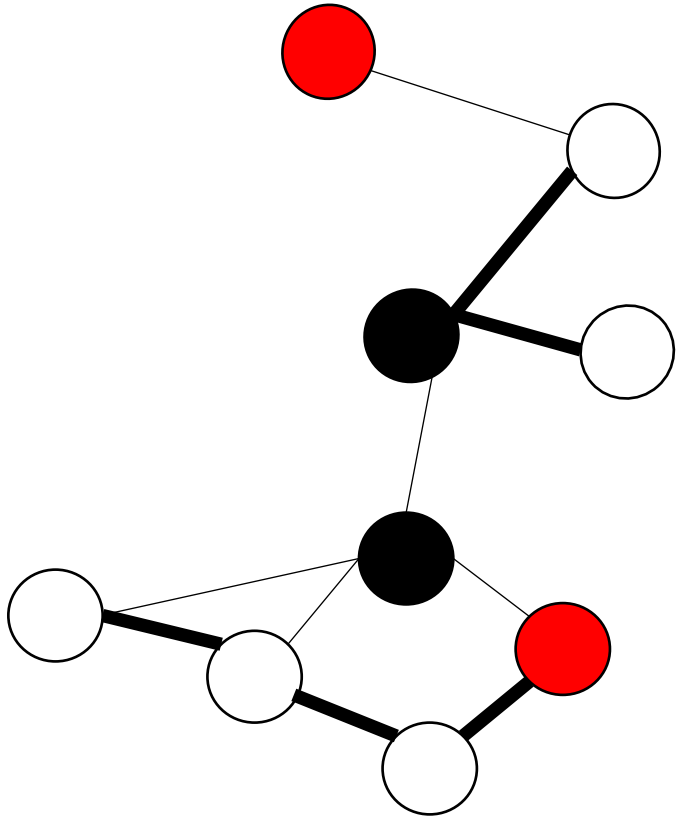
Node classification



Graph Convolutional network



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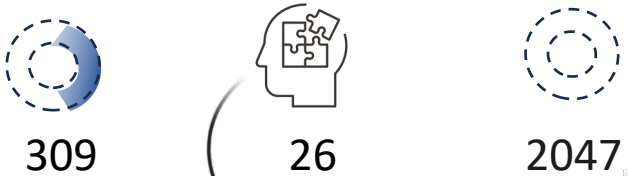
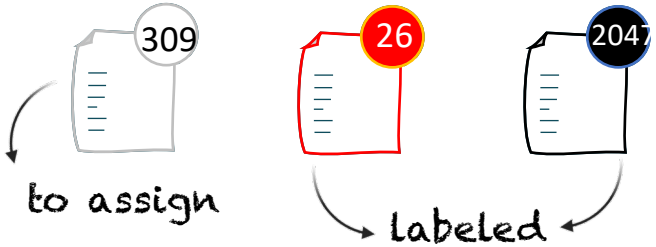


STRING

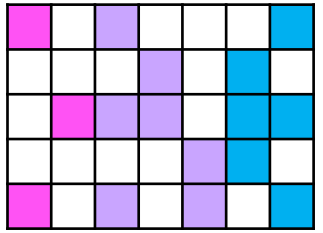
15237 edges

Partial node labelling



Strategy

Edge weights



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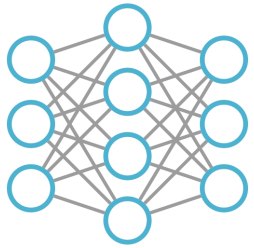

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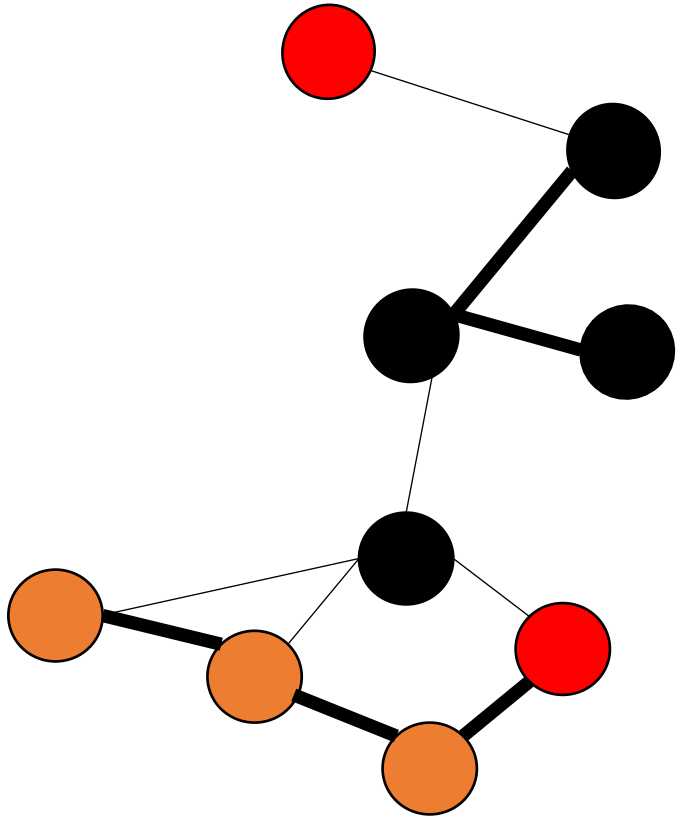

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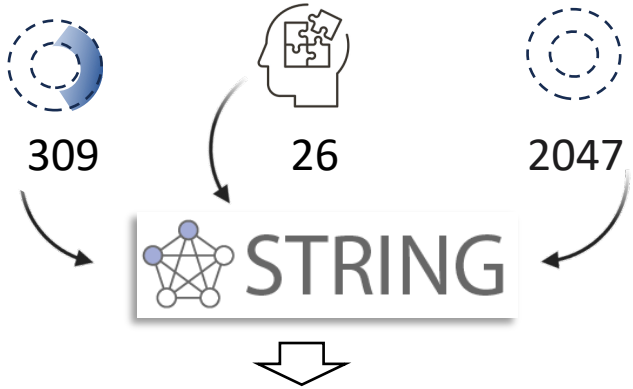

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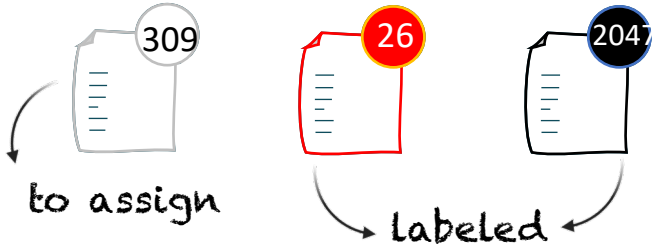


Results

Entire network

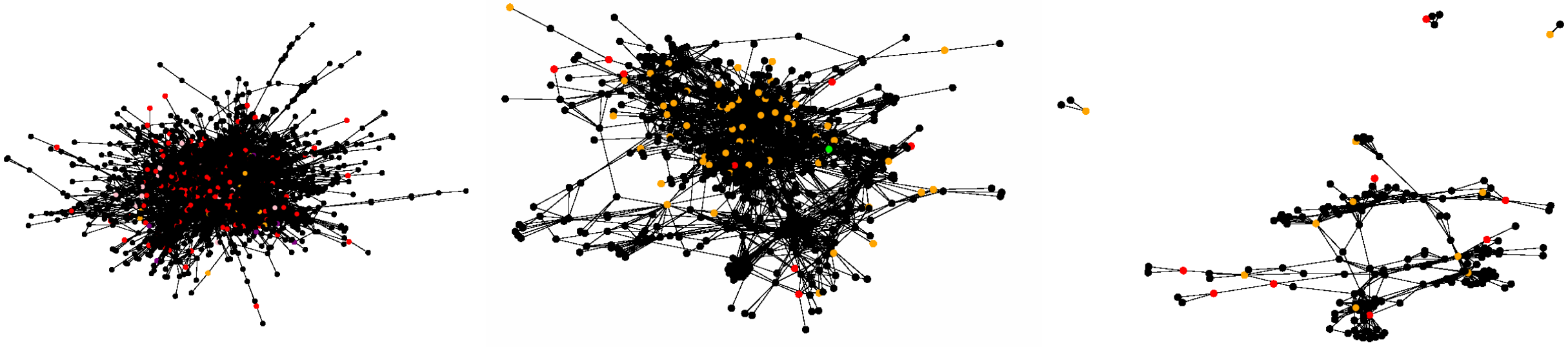
2382 nodes
15237 edges

Second neighbour

nodes
edges

First neighbour

nodes
edges



FMRP

ASD genes from SFARI database

Deregulated in absence of FMRP and predicted as associated to ASD

Predicted as NOT associated to ASD

Results

Entire network

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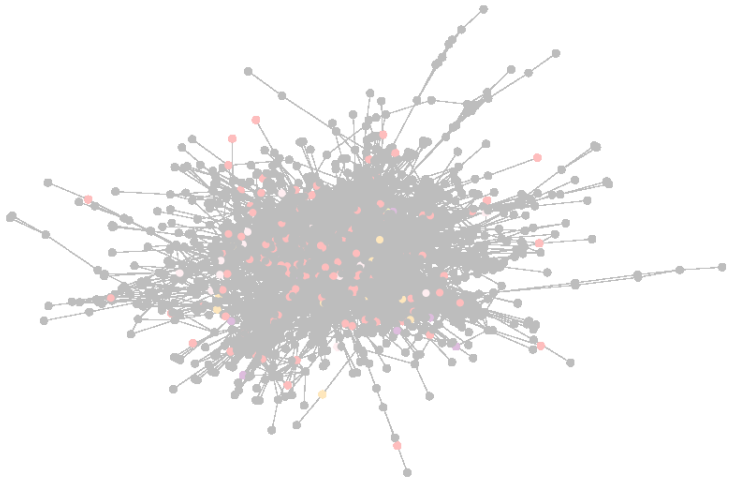
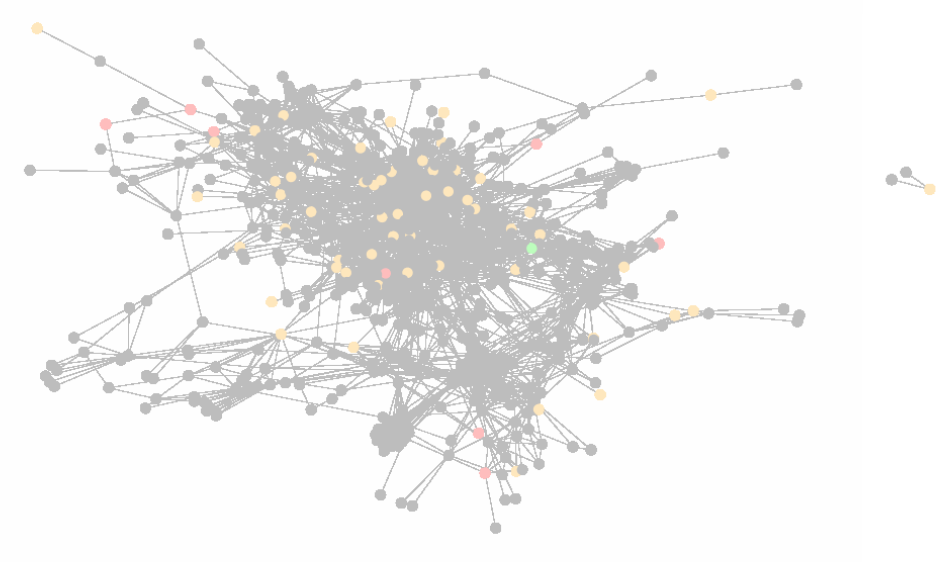
15237 edges



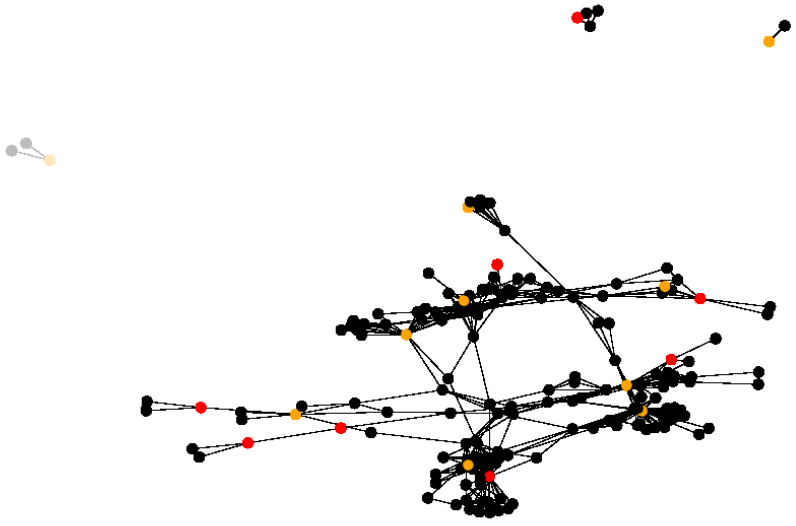
Second neighbour

nodes
edges



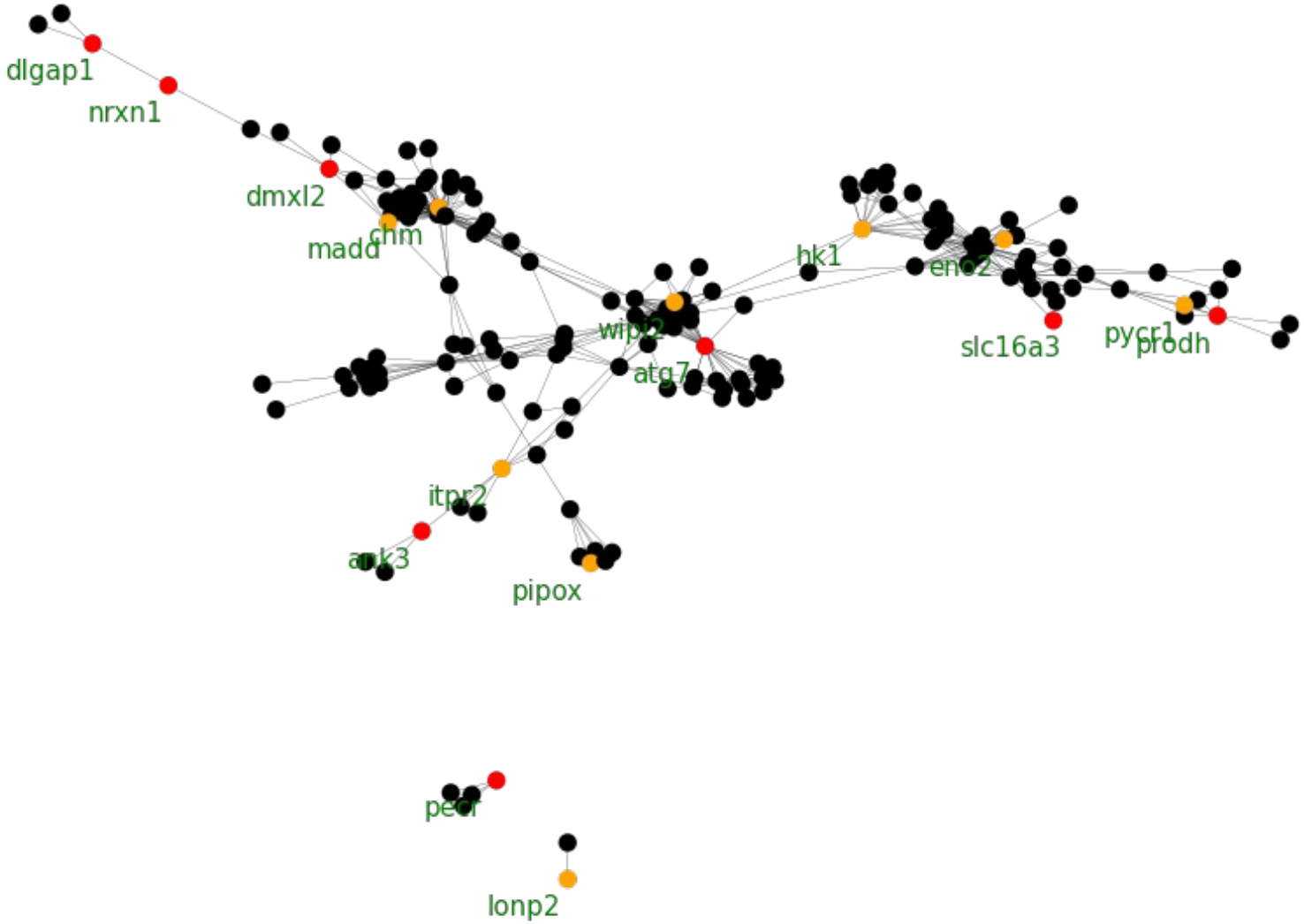
First neighbour

nodes
edges



- FMRP
- ASD genes from SFARI database
- Deregulated in absence of FMRP and predicted as associated to ASD
- Predicted as NOT associated to ASD

Results



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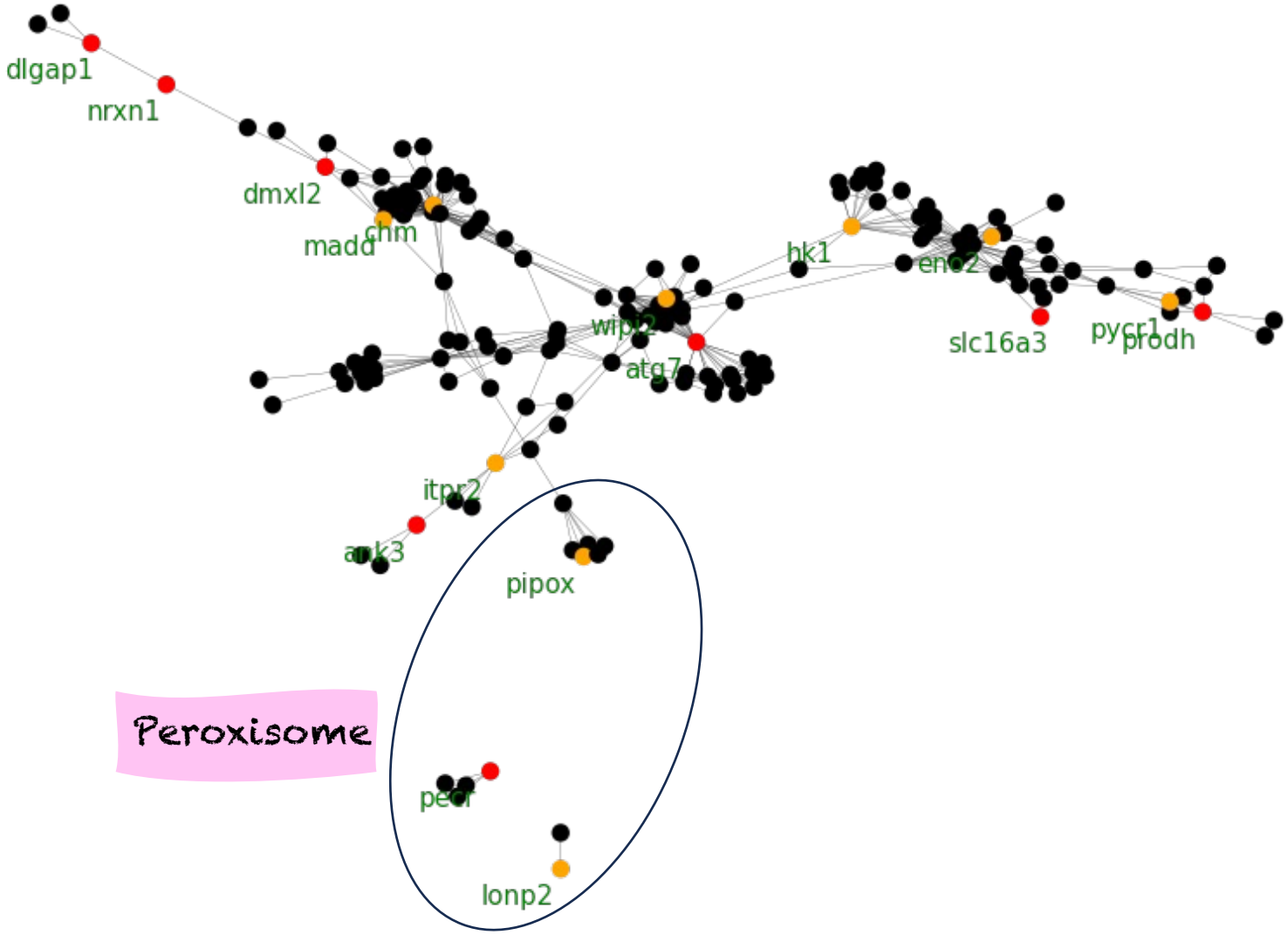

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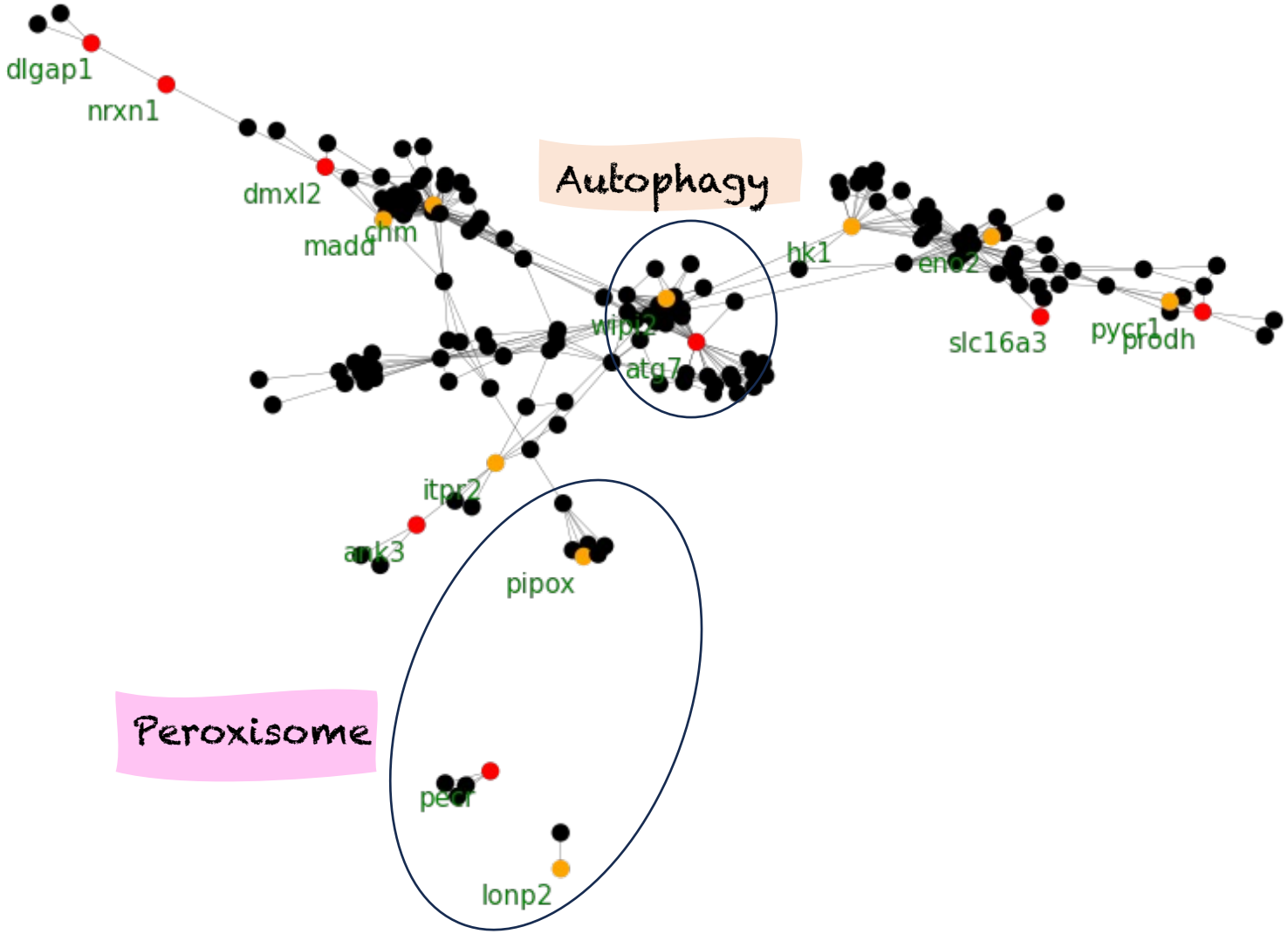

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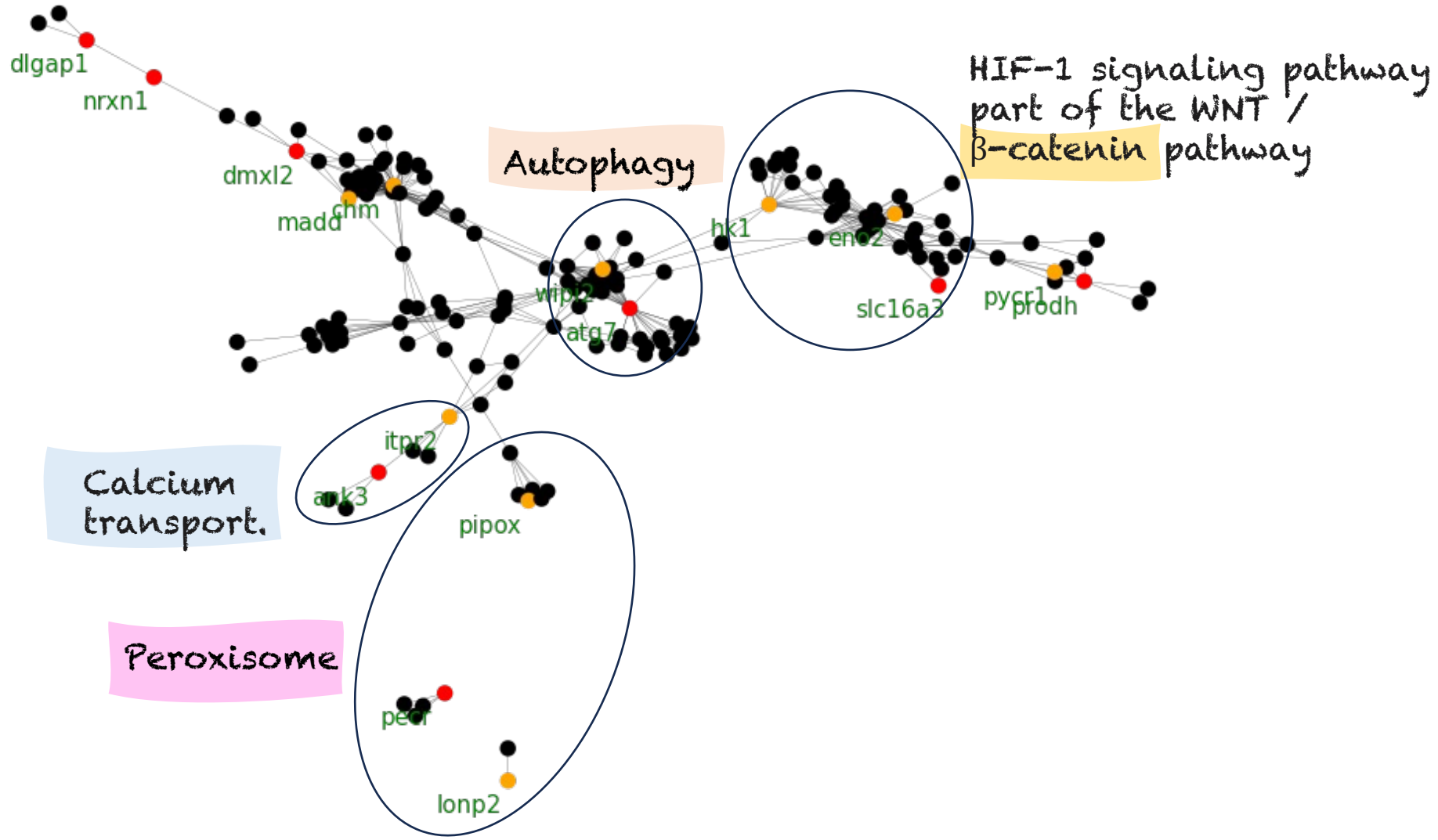

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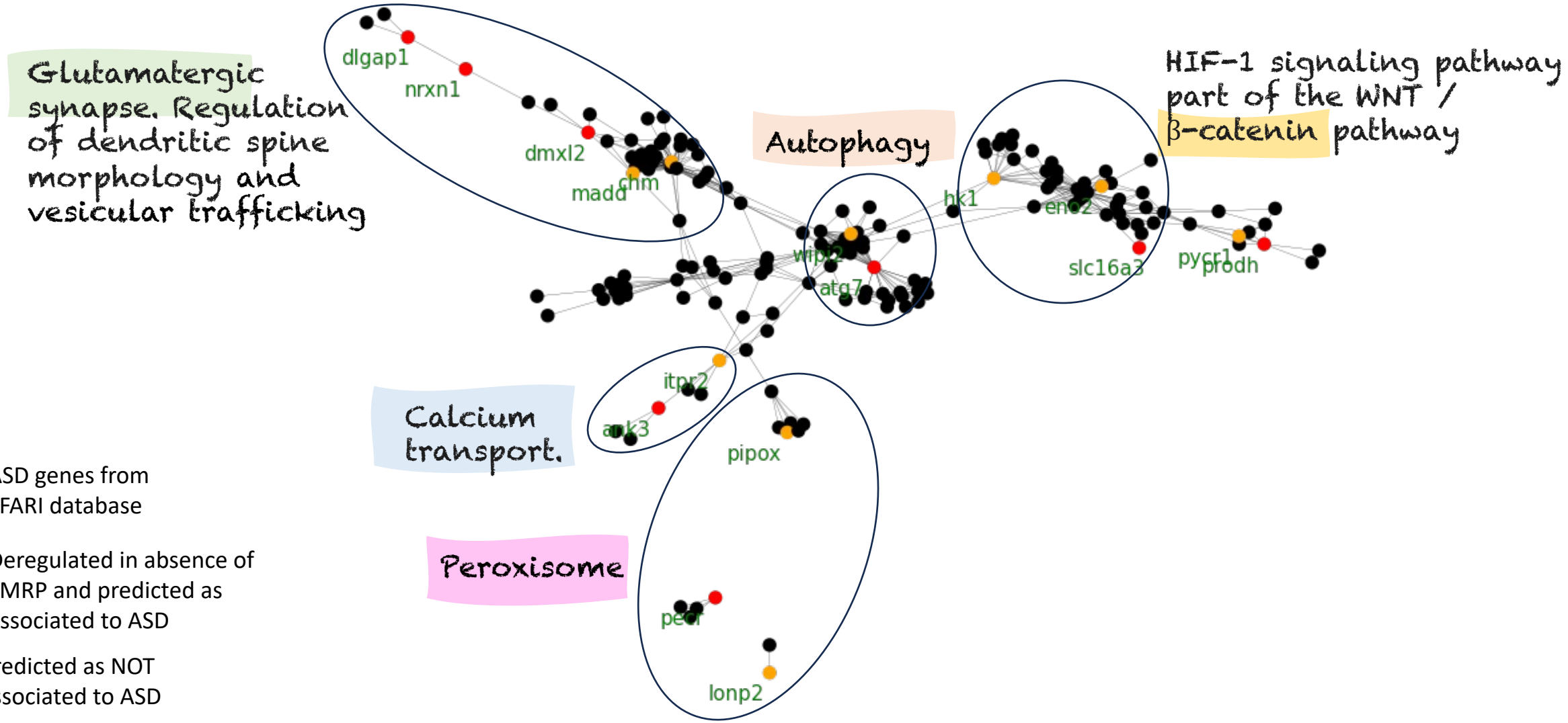
Glutamatergic synapse. Regulation of dendritic spine morphology and vesicular trafficking
dlgap1
nrxn1
dmxl2
madd
chm
Autophagy
wipi2
atg7
HIF-1 signaling pathway part of the WNT / β-catenin pathway
hk1
eno2
slc16a3
pycr1
prodh
Calcium transport.
itpr2
ank3
pipox
Peroxisome
pex1
lonp2
ASD genes from SFARI database
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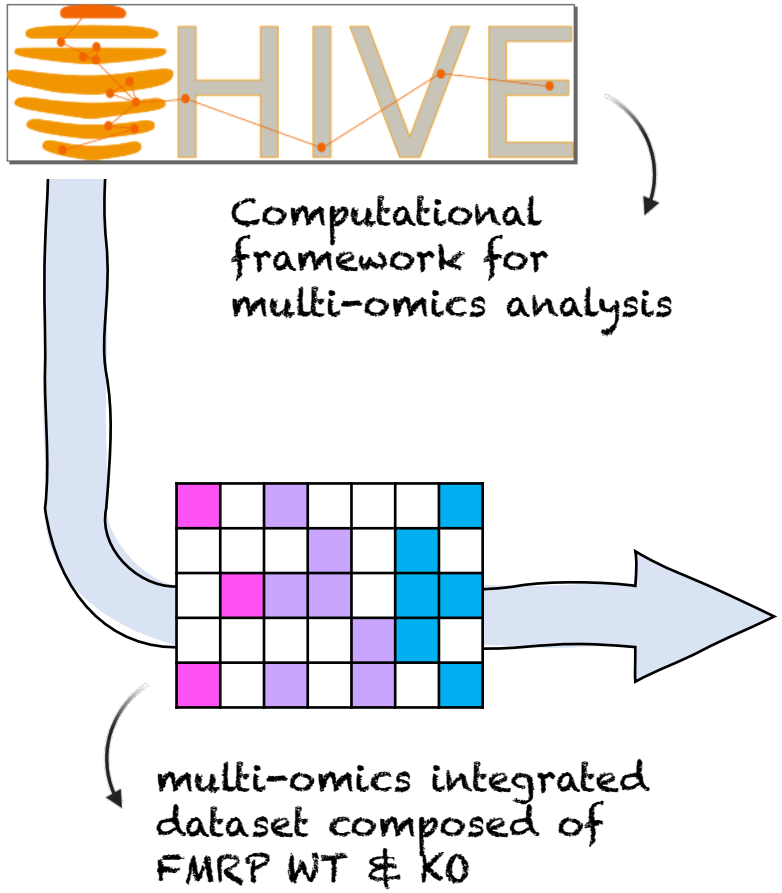
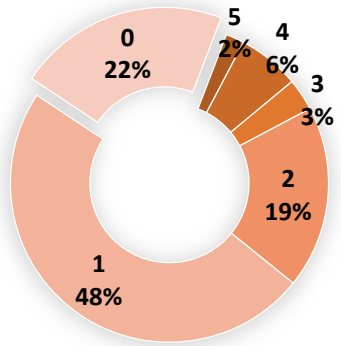
Conclusions

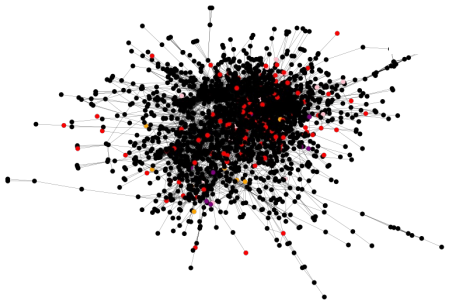


Identify **1229 molecules** deregulated in the absence of FMRP, **22%** of them **not previously** connected to FMRP.

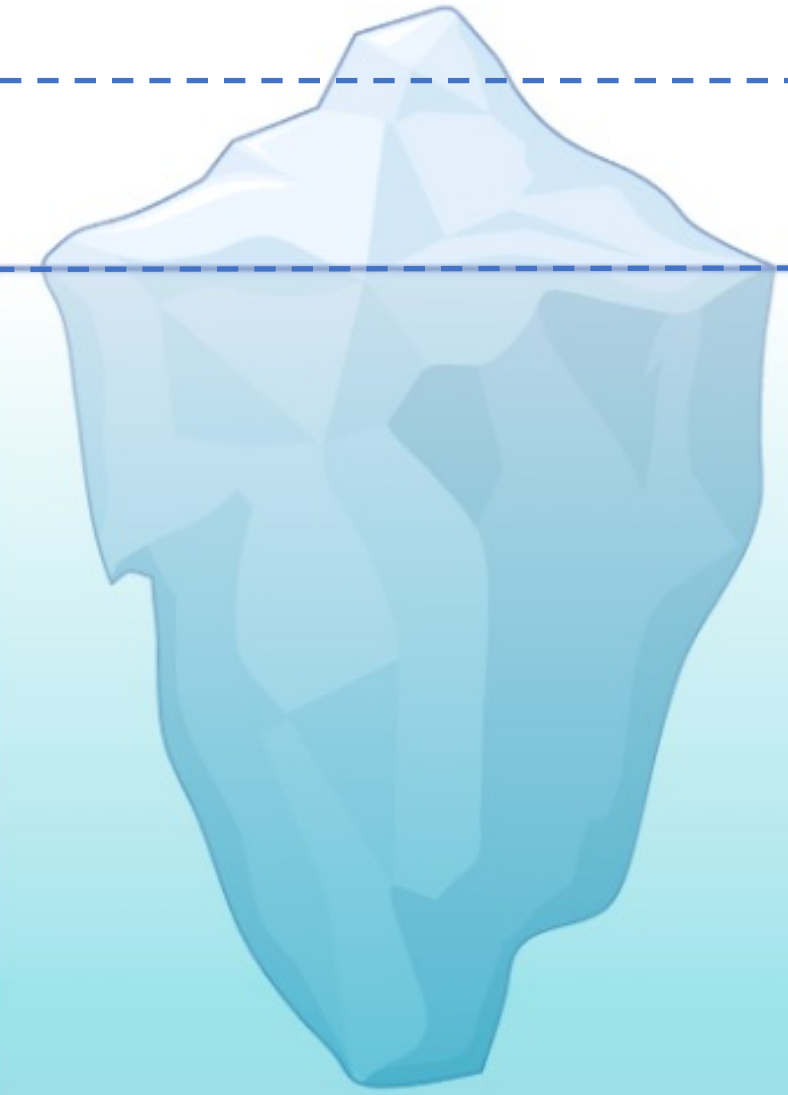


Identify several **novel putative roles** for FMRP including the peroxisome.

Identify of **potential candidates** that link FMRP to ASD.



Take home message



Results showed today

Results obtained with this study

Results that can be potentially obtained by performing

multi-omics,

multi-study,

multi-model

integration analysis.

1 model, 3 omics, 5 datasets

3 models, 7 omics, 43 datasets

Complete understanding of the role of FMRP in neuronal physiology.

Acknowledgements

Giulia Calia
Wassila Kathir
Mame Seynabou Fall
Anjana Bhat
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Youssef Boulaimen
Gauthier Marcovich

Carole Gwizdek
Barbara Bardoni
Jeromine Carret

All the members of the team "RNA Metabolism and Neurodevelopmental Disorders"