Pathway of a rare disease

Neurodegeneration with brain iron accumulation

NBIA

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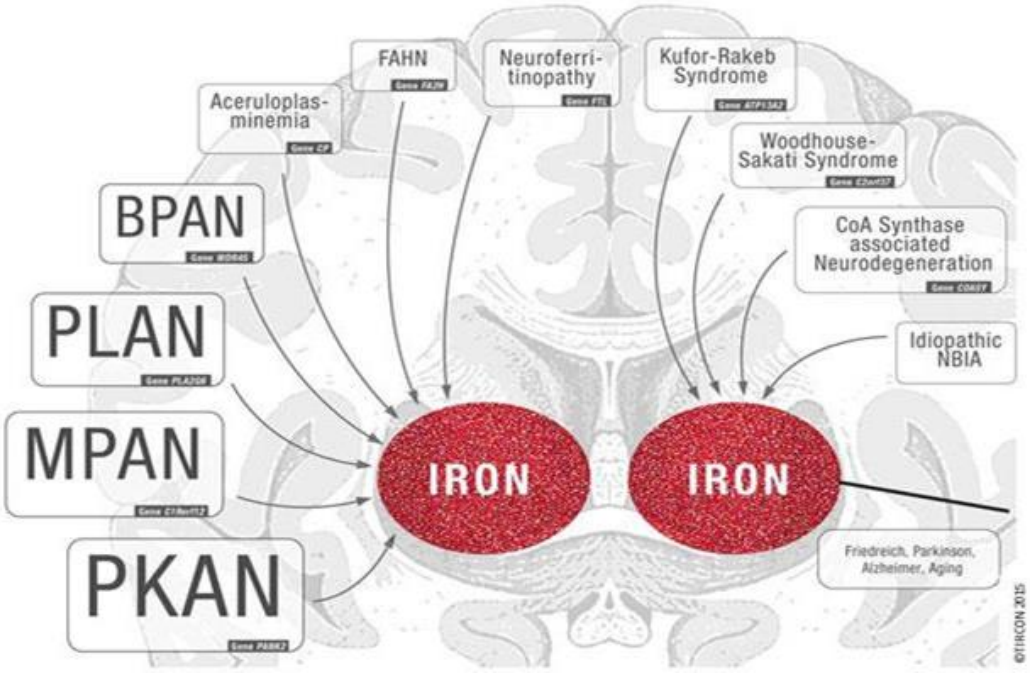
Maastricht University

What is NBIA?



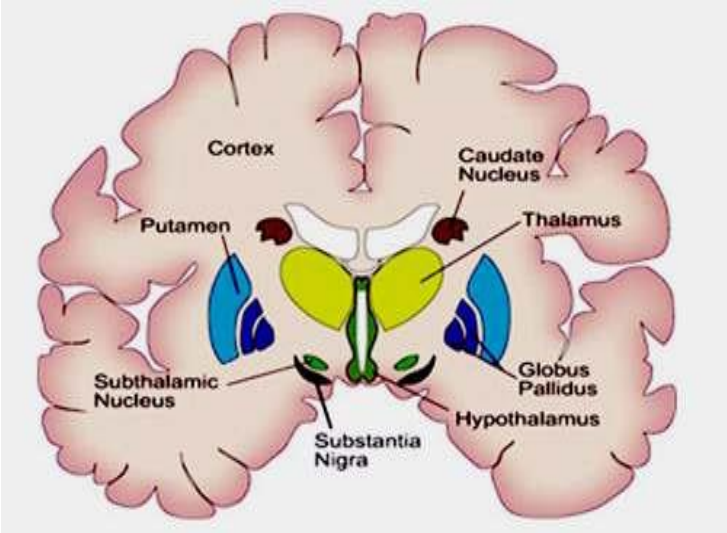
- Rare neurodegenerative disease
  1-3 per 1,000,000 individuals
- 12 subtypes
- Before 2001 Hallervorden-Spatz syndrome
- Phenotype similar to Rett syndrome

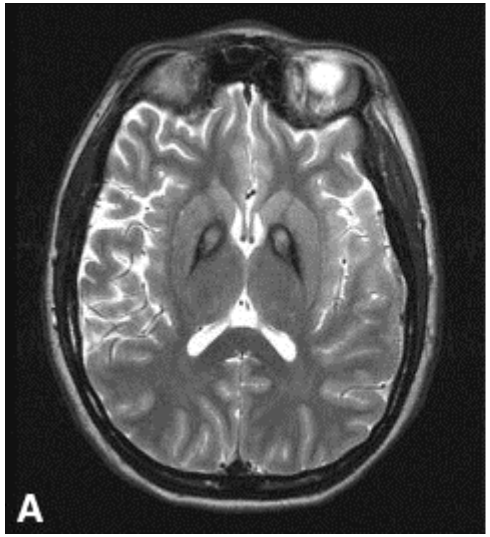
http://www.nbiaalliance.org/

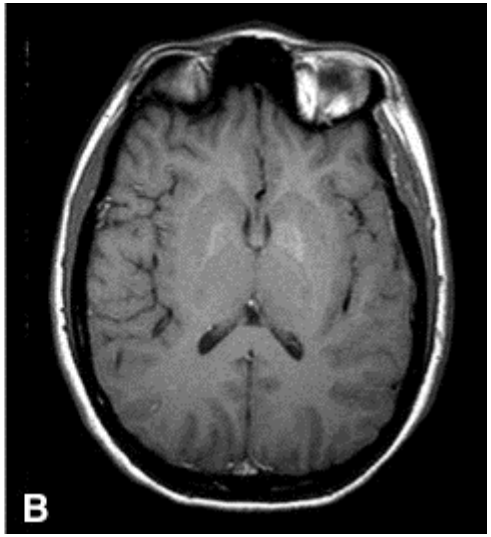
Bokhari MR, Bokhari SRA. Hallervorden Spatz Disease (Pantothenate Kinase-Associated Neurodegeneration, PKAN) [Updated 2018 Oct 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2019 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK430689/

Phenotype

- Excessive iron (basal ganglia structures)
- General developmental and intellectual disabilities
- Seizures, parkinsonism



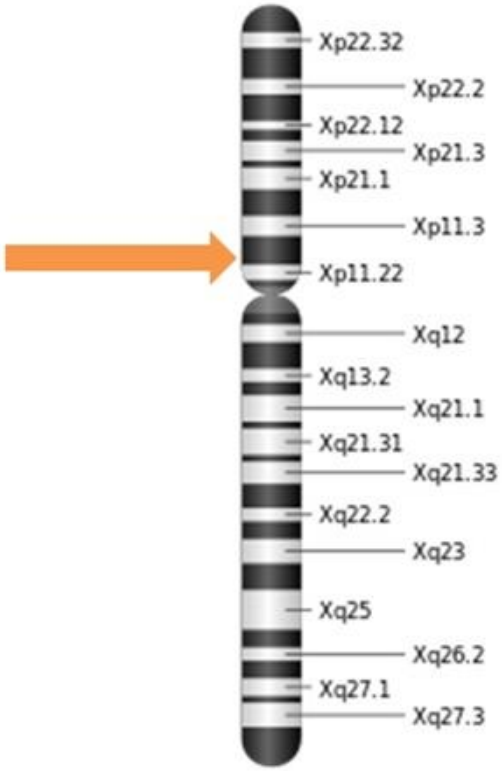




Measurement of Brain Iron Distribution in Hallevorden-Spatz Syndrome - Scientific Figure on ResearchGate. Available from: https://www.researchgate.net/figure/The-standard-MRI-studies-of-PKAN-patients-h central_fig4_41124744 [accessed 30 Apr, 2019]

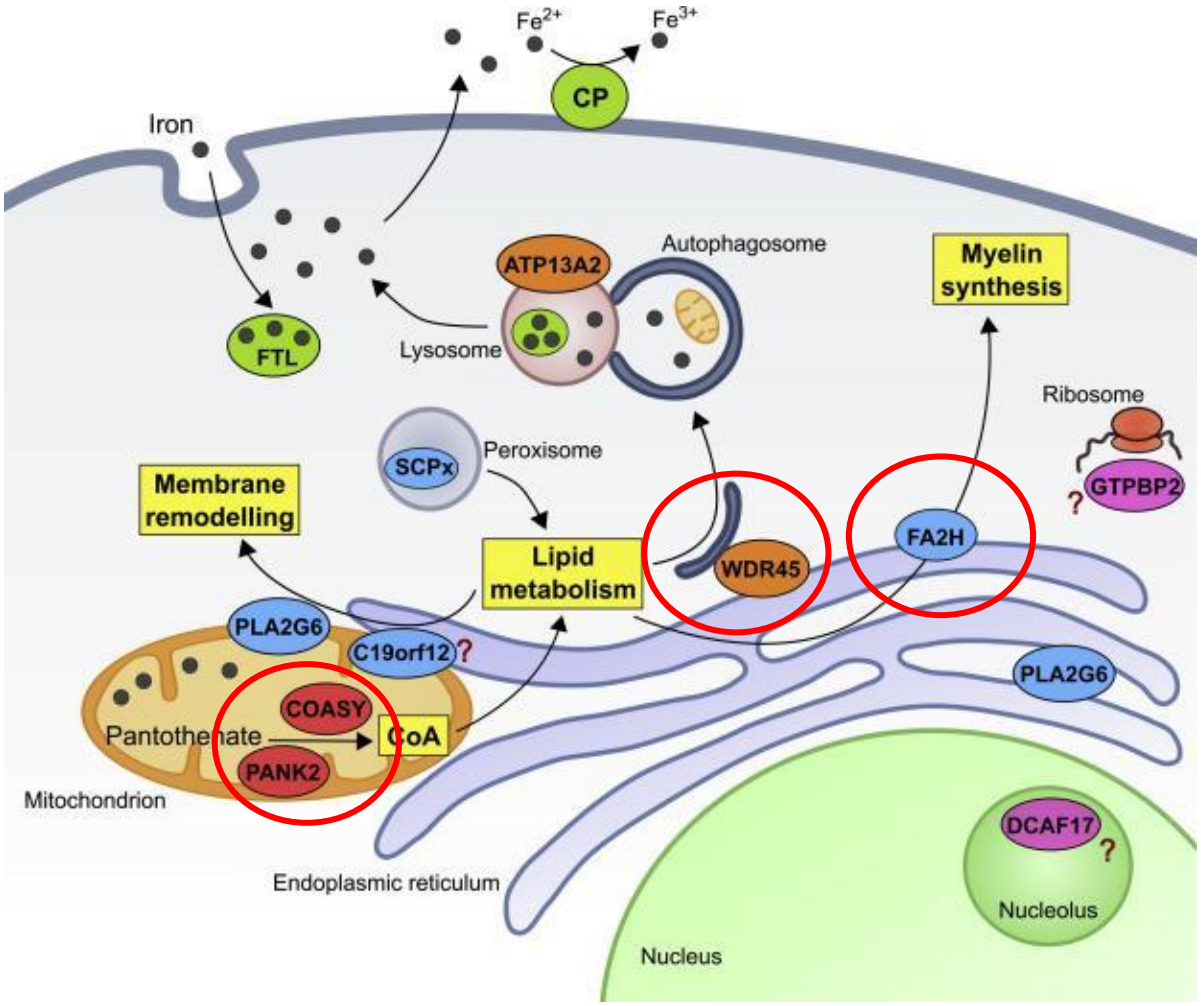
Beta-propeller associated neurodegeneration

- BPAN
- WDR45
- Prevalence: <1 / 1,000,000
- Formation of autophagosome



https://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=21922&Disease_Disease_Search_diseaseGroup=300894&Disease_Disease_Search_diseaseType=OMIM&Disease(s)/group%20of%20diseases=Beta-propeller-protein-associated-neurodegeneration&title=Beta-propeller%20protein-

Cellular location and function



Maastricht University

Di Meo, I., & Tiranti, V. (2018). Classification and molecular pathogenesis of NBIA syndromes. *european journal of paediatric neurology*, *22*(2), 272-284.

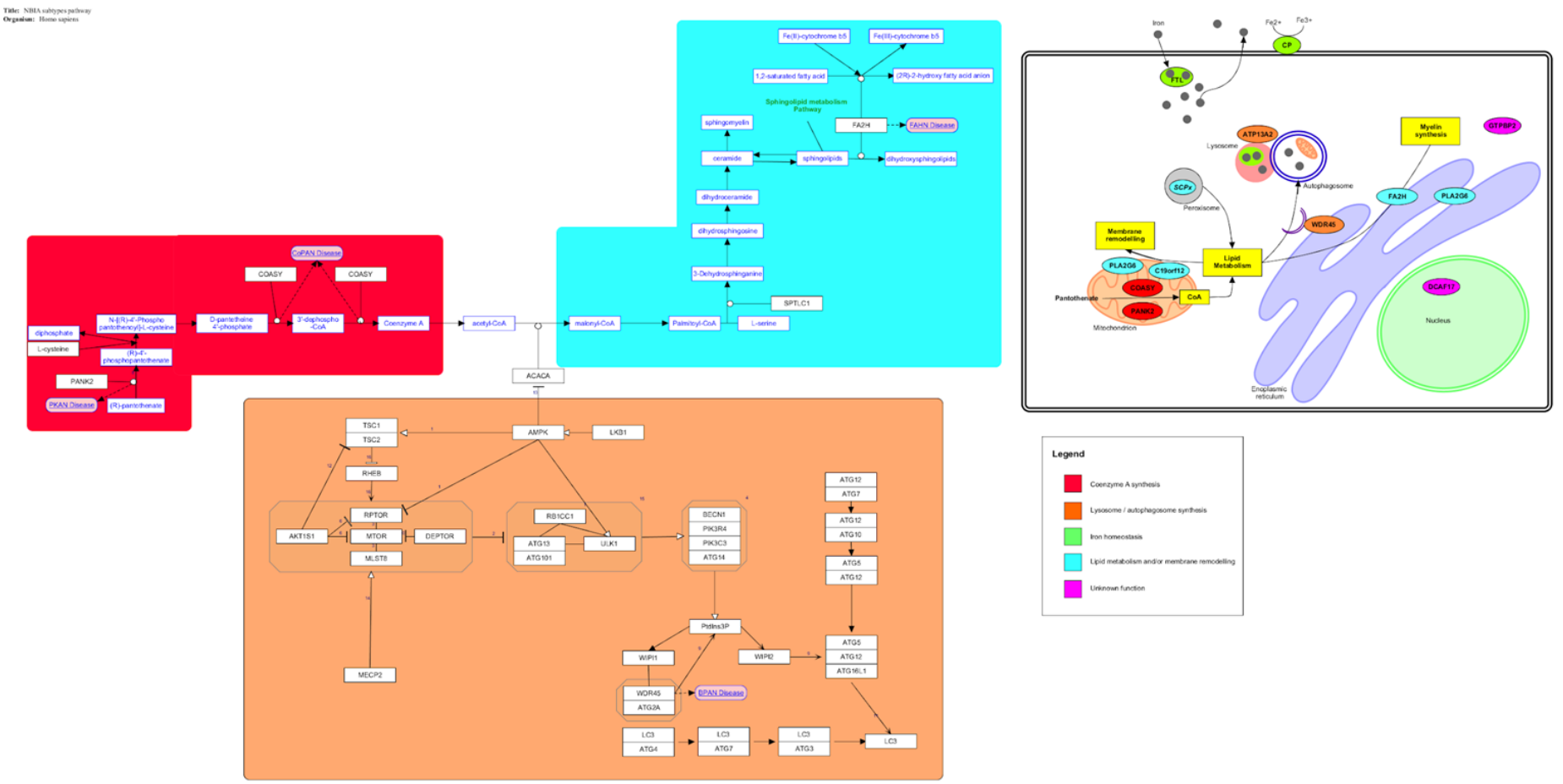
Research Question

What is the role of WDR45 and other NBIA causing genes in the pathological pathway resulting in the phenotype?

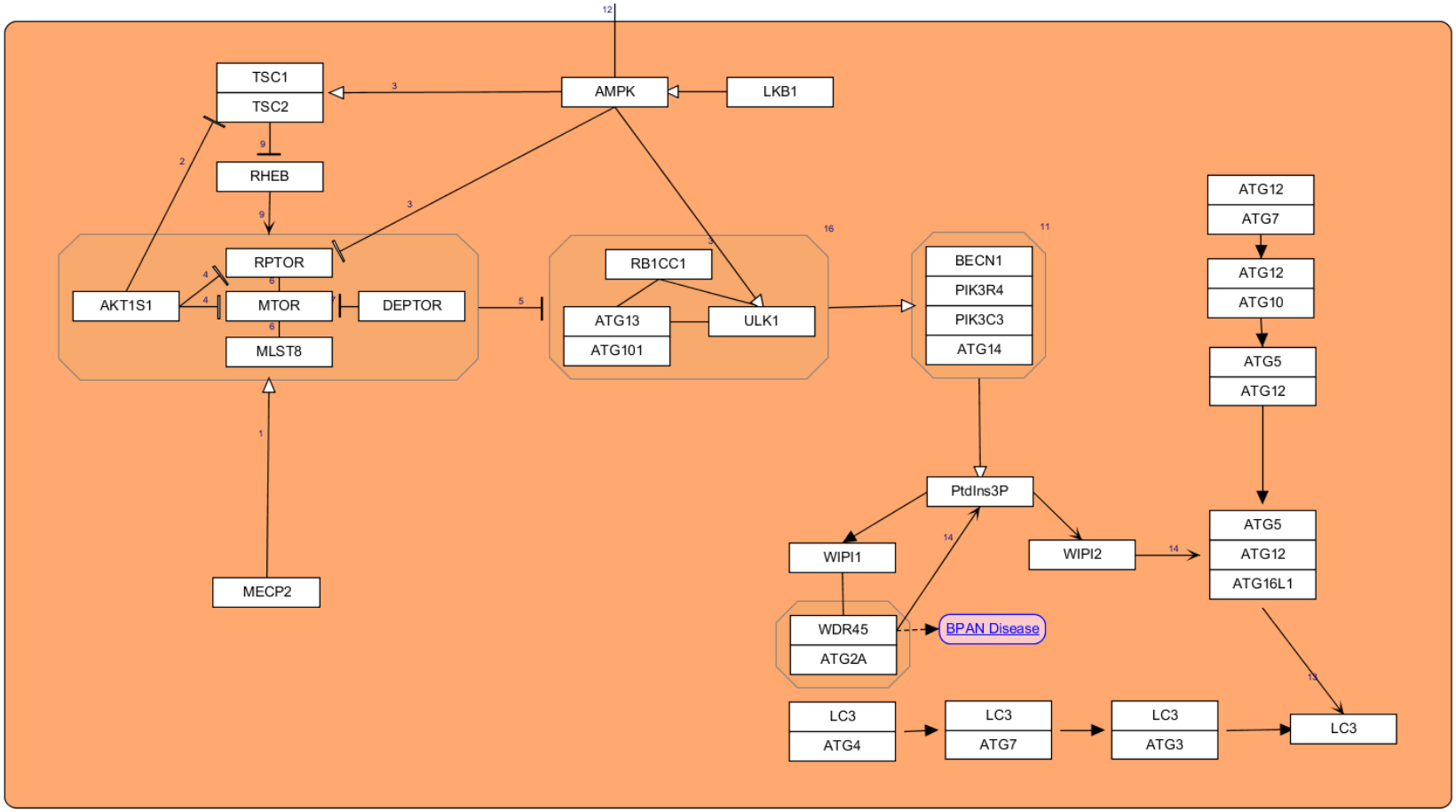
Methods

Literature research
Creating pathway
Expression data
Pathway analysis
Gene ontology analysis

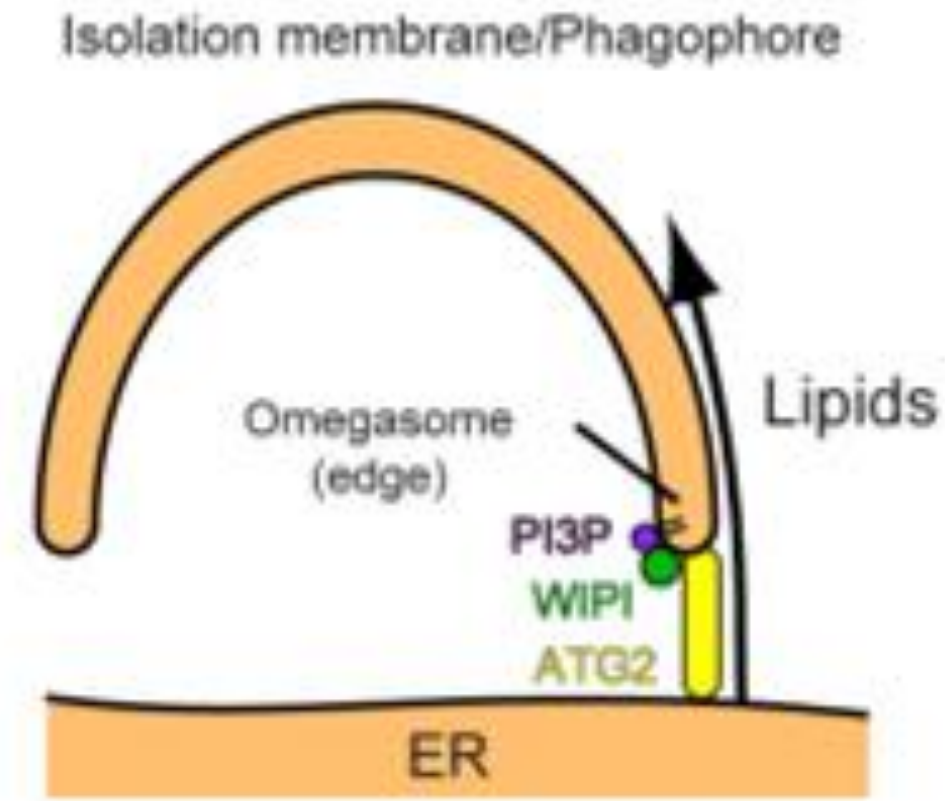
NBIA subtype pathway



Betta-propeller associated neurodegeneration

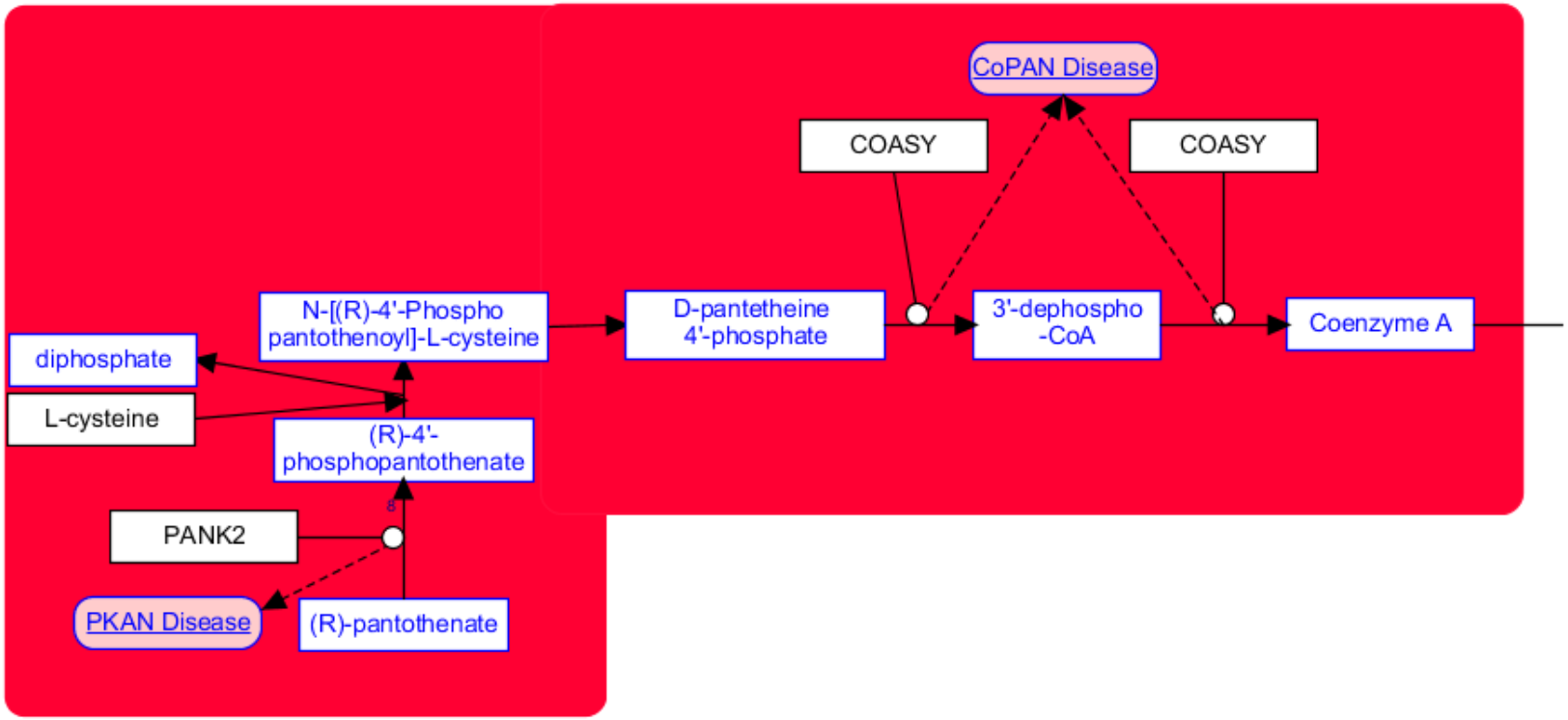


Function of WDR45

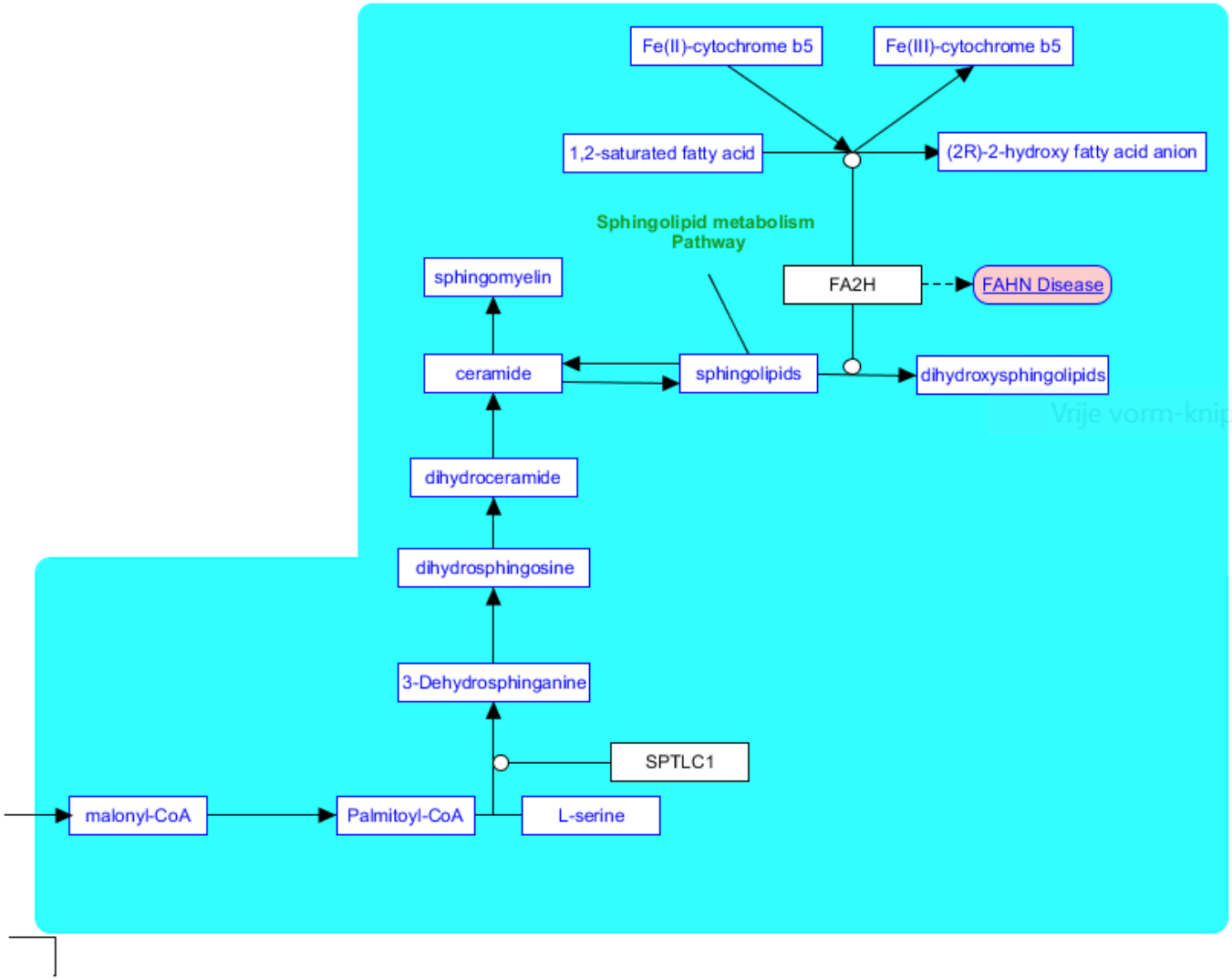


Wan, H., Wang, Q., Chen, X., Zeng, Q., Shao, Y., Fang, H., ... & Diao, M. (2019). WDR45 contributes to neurodegeneration through regulation of ER homeostasis and neuronal death. *Autophagy*, (just-accepted).

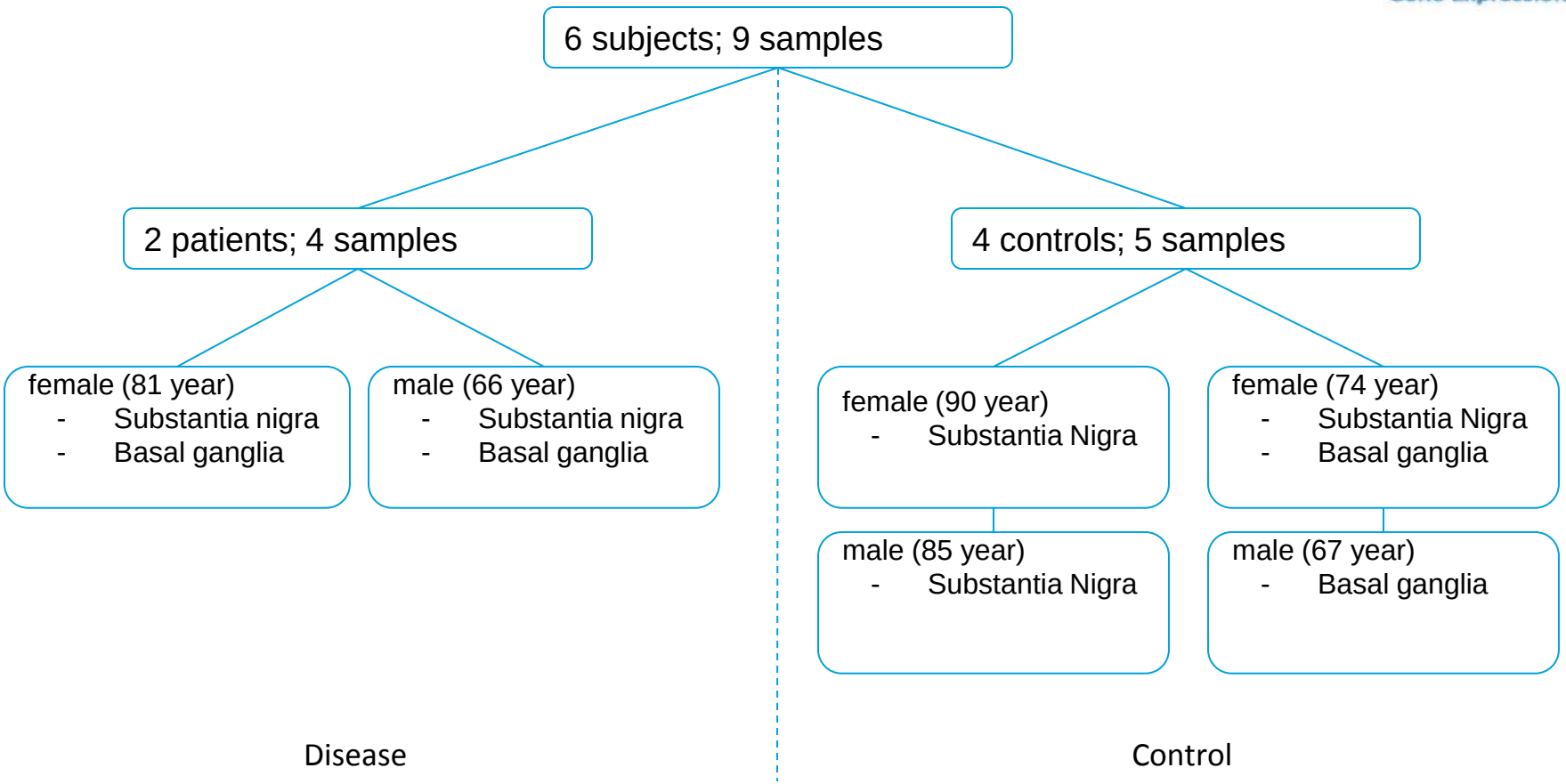
PKAN & CoPAN


CoPAN Disease
COASY
COASY
N-[(R)-4'-Phospho pantothenoyl]-L-cysteine
D-pantetheine 4'-phosphate
3'-dephospho -CoA
Coenzyme A
diphosphate
L-cysteine
(R)-4'-phosphopantothenate
PANK2
PKAN Disease
(R)-pantothenate

FAHN


Fe(II)-cytochrome b5
Fe(III)-cytochrome b5
1,2-saturated fatty acid
(2R)-2-hydroxy fatty acid anion
Sphingolipid metabolism Pathway
sphingomyelin
FA2H
FAHN Disease
ceramide
sphingolipids
dihydroxysphingolipids
dihydroceramide
dihydrosphingosine
3-Dehydrosphinganine
SPTLC1
malonyl-CoA
Palmitoyl-CoA
L-serine

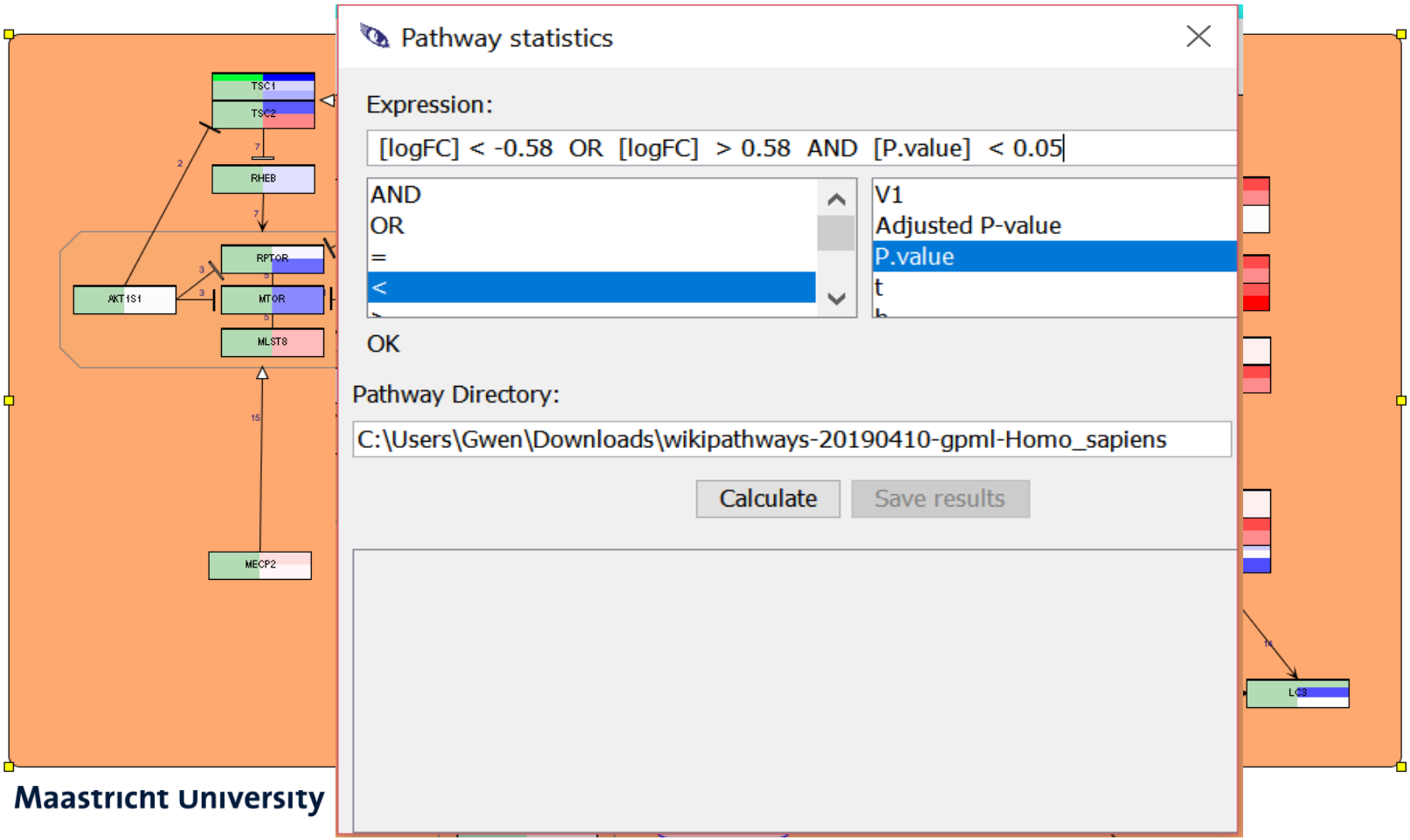
Expression dataset



Pathway analysis

PathVisio

Import expression data | Visualization | Pathway analysis



Pathway analysis

Pathway	Z-score	P-value	positive (r)
lung fibrosis	3.12	0.007	8
TWEAK signaling pathway	3.09	0.008	6
cysteine and methionine catabolism	3.07	0.01	3
fetal androgen synthesis	2.91	0.005	3
cell differentiation-index	2.74	0.012	5

criteria: Z-score > 1.96 and positive (r) ≥ 3

Heidari, M., Johnstone, D. M., Bassett, B., Graham, R. M., Chua, A. C. G., House, M. J., ... & Olynyk, J. K. (2016). Brain iron accumulation affects myelin-related molecular systems implicated in a rare neurogenetic disease family with neuropsychiatric features. *Molecular psychiatry*, *21*(11), 1599.

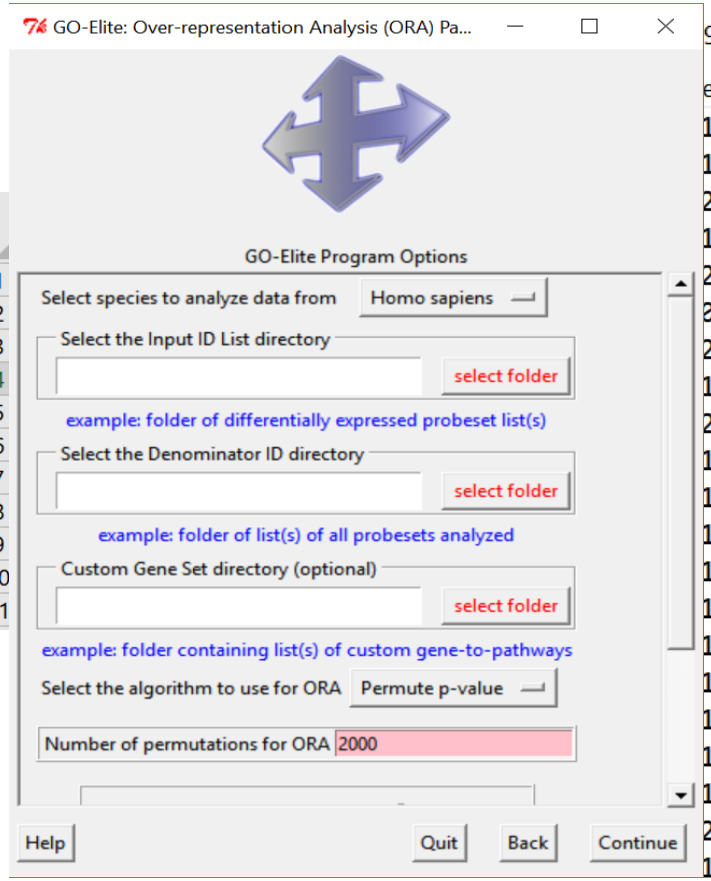
GO analysis of genes found in pathway analysis

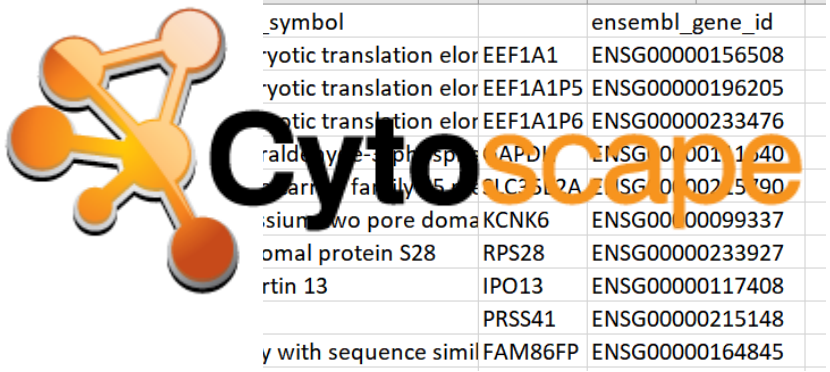
56 genes differentially expressed
- 28 upregulated
- 28 downregulated

14 associated with immune system
- pro-inflammatory genes upregulated
- anti-inflammatory genes downregulated

Gene ontology analysis

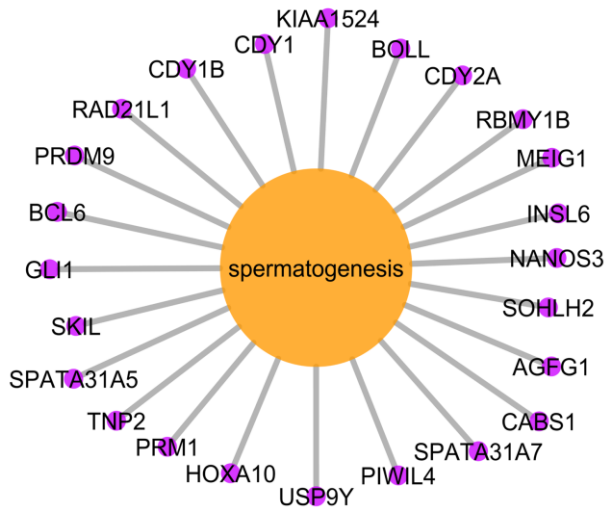
Filter dataset | Prepare datafiles | GO_elite

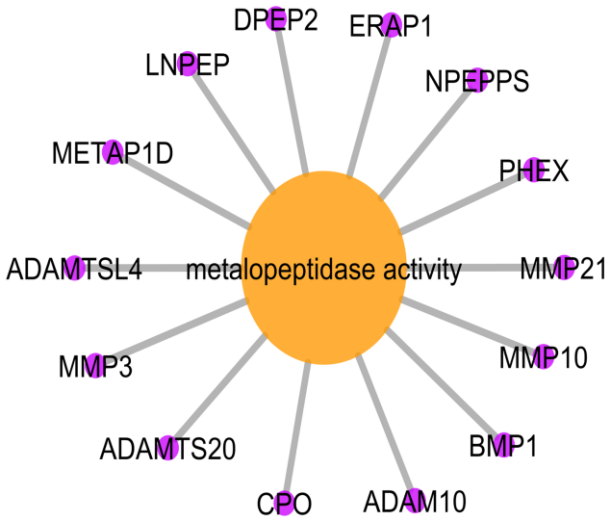


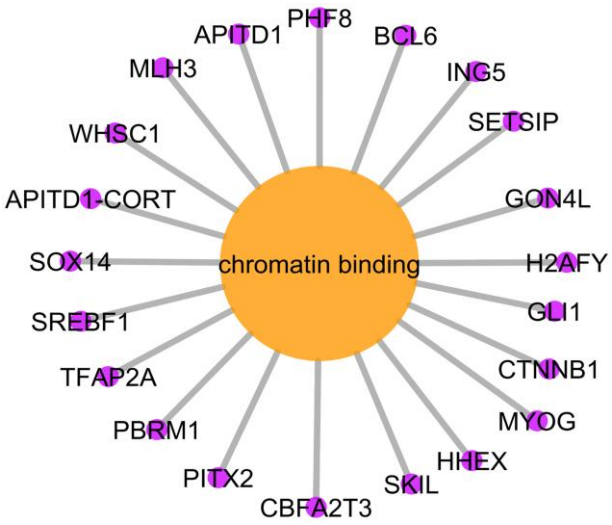


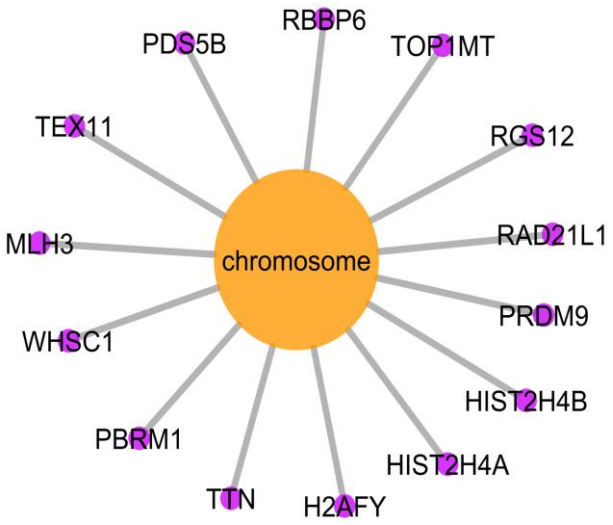
I	J	K	L
_symbol		ensembl_gene_id	
yotic translation elor	EEF1A1	ENSG00000156508	
yotic translation elor	EEF1A1P5	ENSG00000196205	
otic translation elor	EEF1A1P6	ENSG00000233476	
wo pore doma	KCNK6	ENSG00000099337	
omal protein S28	RPS28	ENSG00000233927	
rtin 13	IPO13	ENSG00000117408	
	PRSS41	ENSG00000215148	
y with sequence simil	FAM86FP	ENSG00000164845	

Gene ontology analysis - upregulated genes

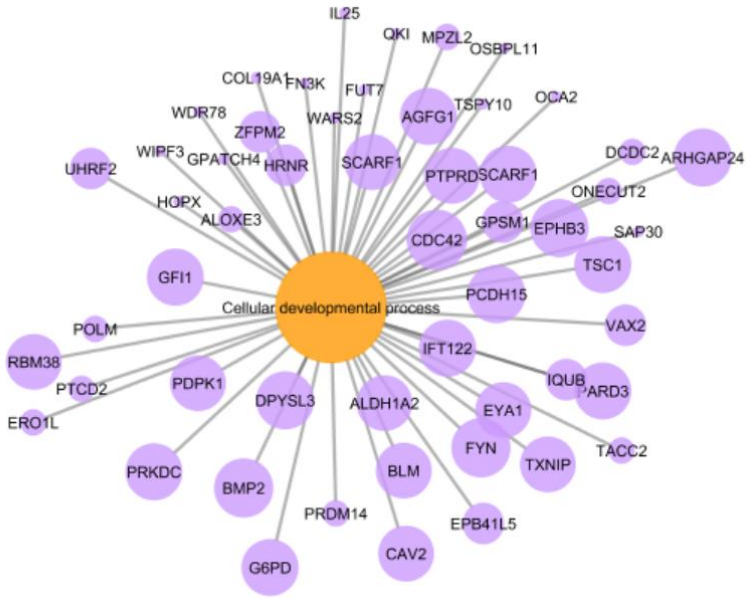


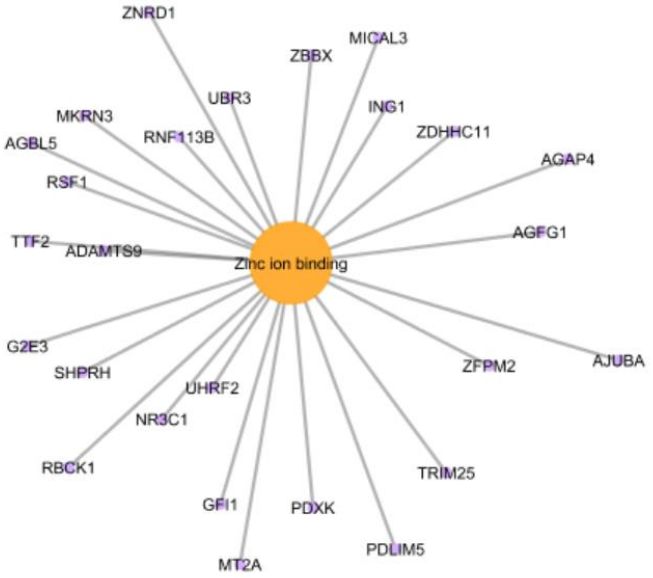


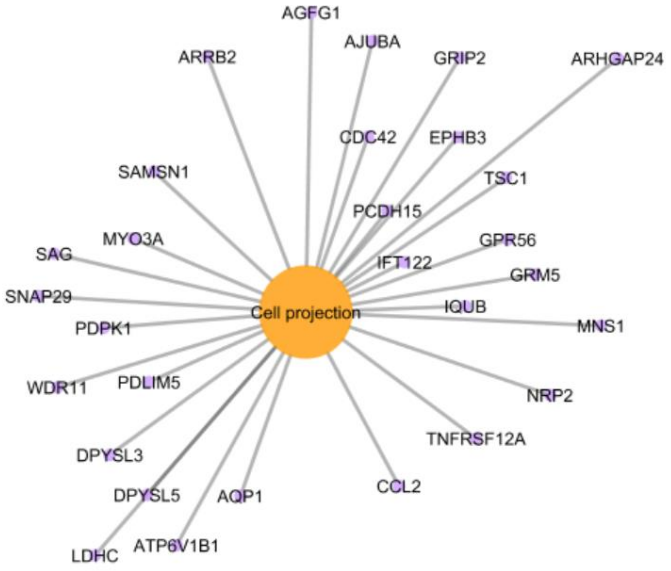


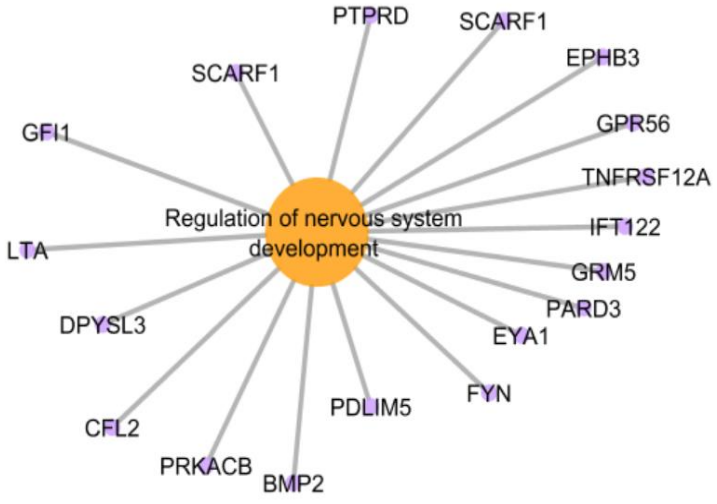


Gene ontology analysis - downregulated genes









Weaknesses of the study

- No data specific for BPAN
- Not enough data to seperate groups based on sex, disease, and tissue type
- Some genes have a negative as well as positive LogFC within the dataset
- Not enough knowledge yet.

Strengths of the study

- BPAN, CoPAN, PANK and FAHN could be visualized in one pathway.

- Inflammation seems to be present in the brain tissues

Future perspective

- BPAN specific data for the pathway analysis
- Add other subtypes to the pathway
- Look into the function of WDR45, and the protein interactions
- Use mice model or cell cultures to look into the inflammation in the brain

Acknowledgements

I would like to thank

Friederike Ehrhart (supervisor)
Denise Slenter

Other students!

Thank you for the attention!
Questions?