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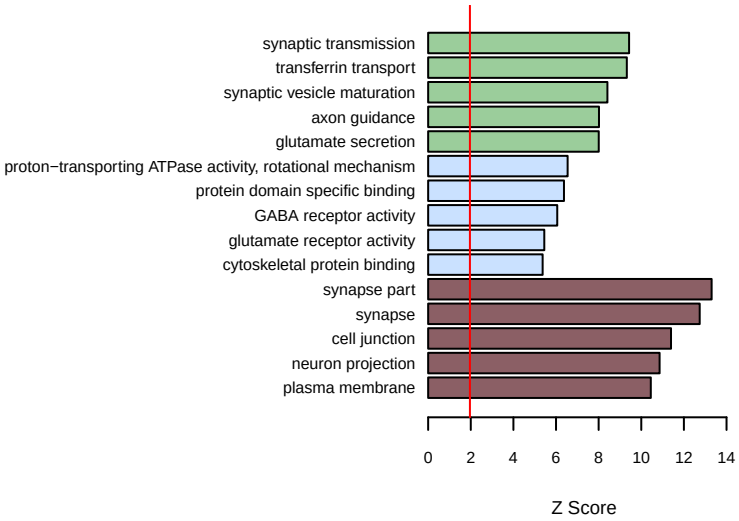
Supplementary information

Large-scale deep multi-layer analysis of Alzheimer's disease brain reveals strong proteomic disease-related changes not observed at the RNA level

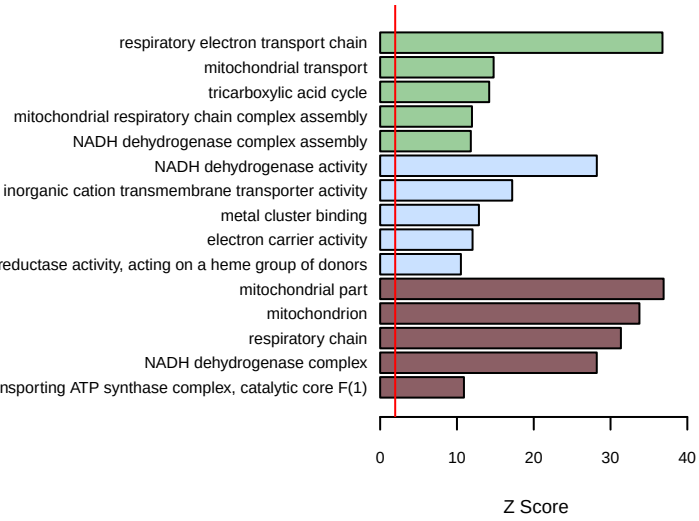
In the format provided by the authors and unedited

Ontology Types
Biological Process
Molecular Function
Cellular Component

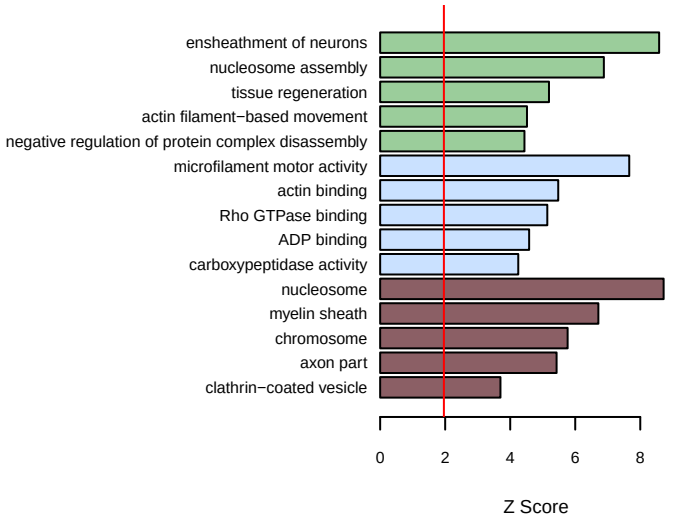
M1 turquoise



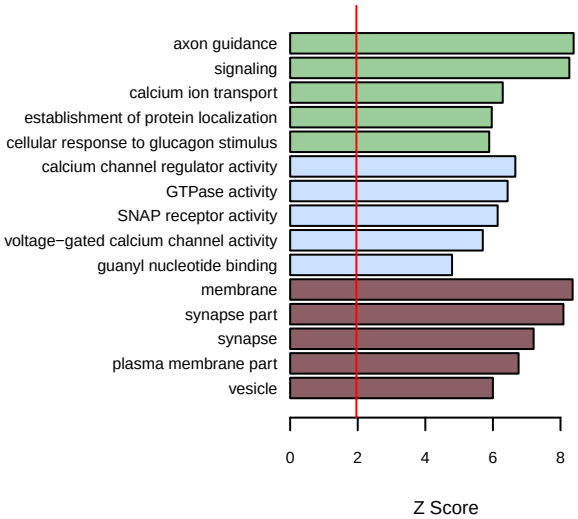
M2 blue



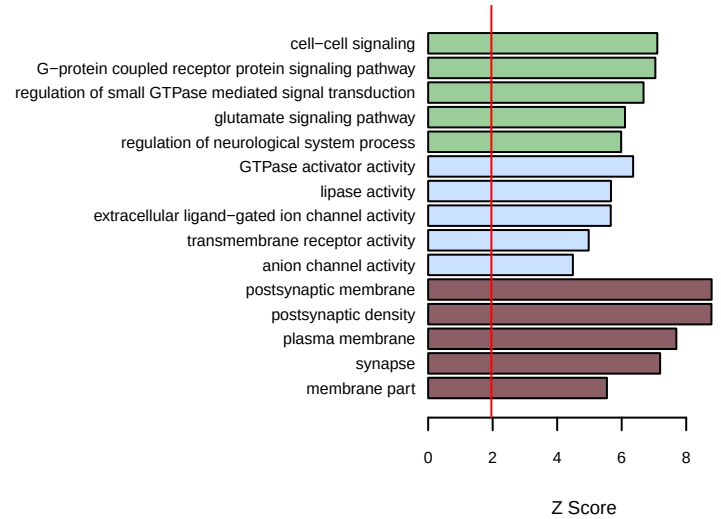
M3 brown

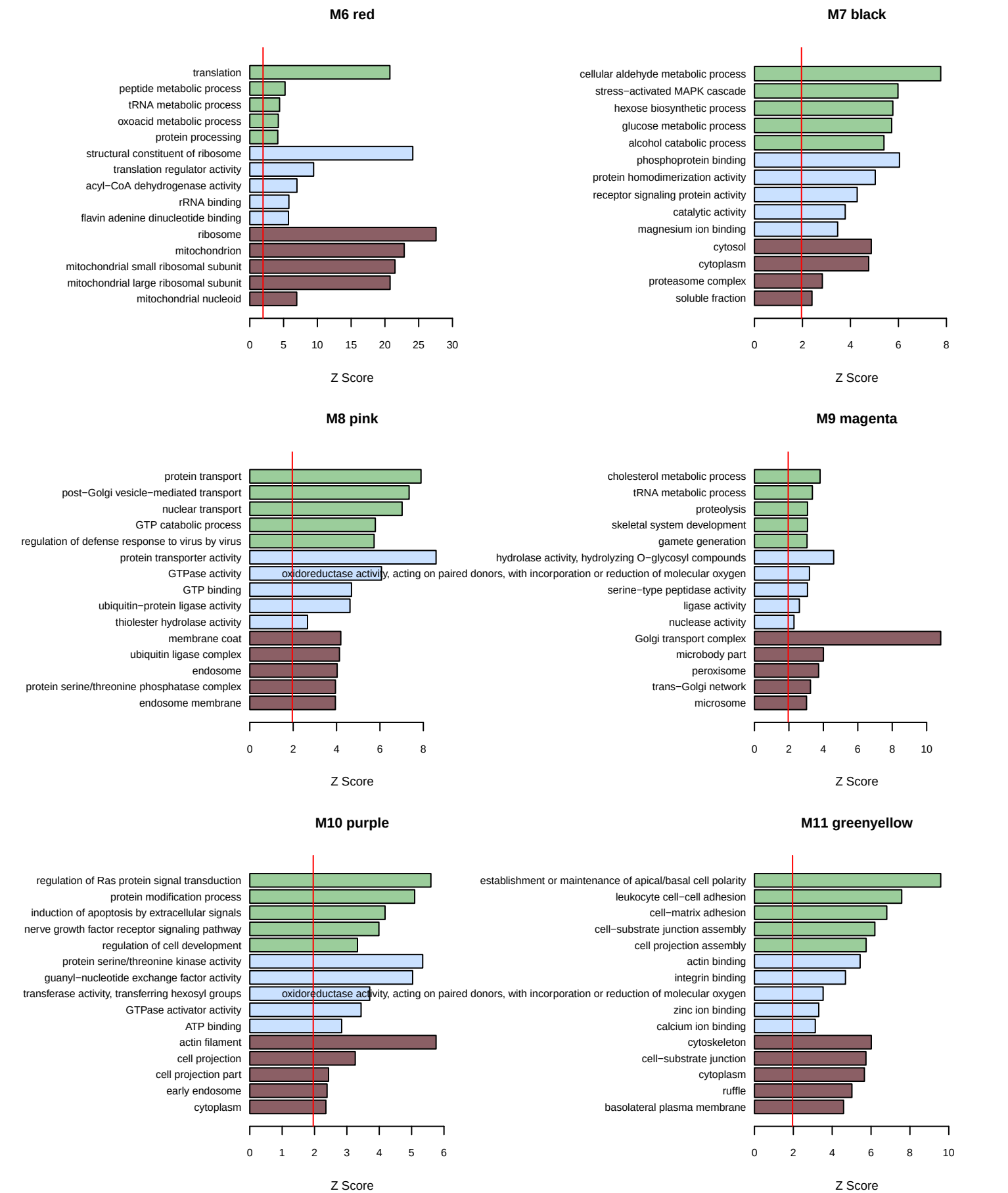


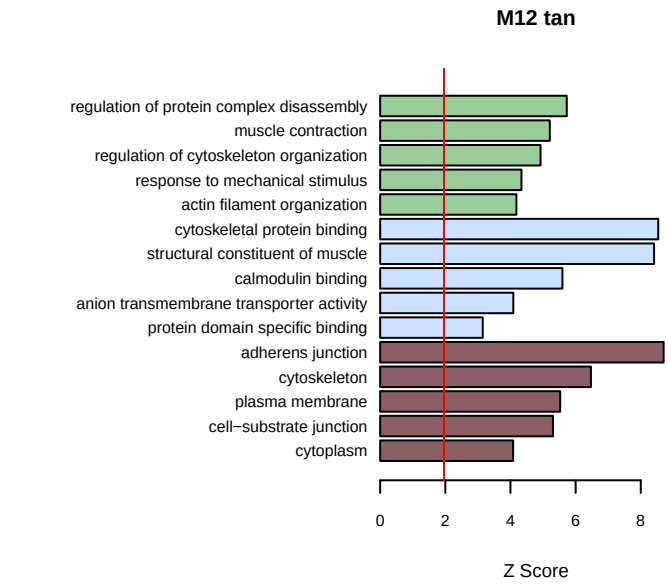
M4 yellow

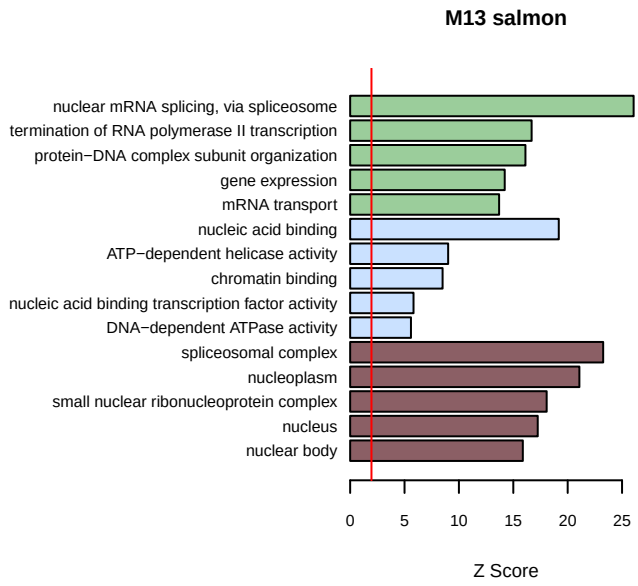


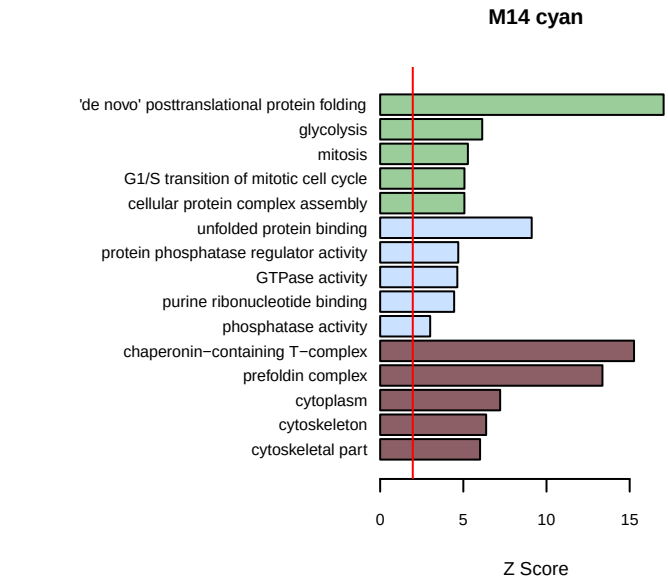
M5 green

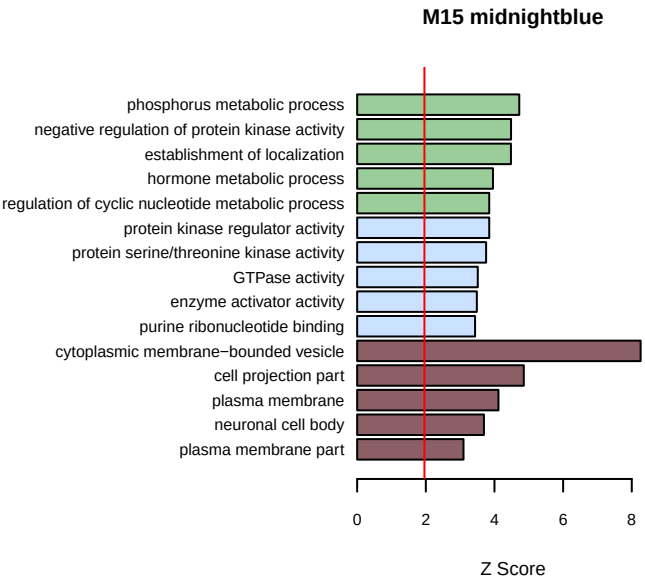


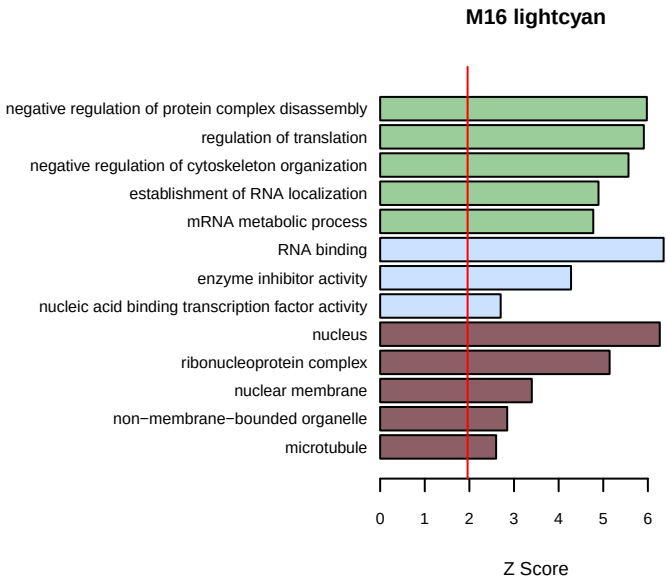

M6 red
translation
peptide metabolic process
tRNA metabolic process
oxoacid metabolic process
protein processing
structural constituent of ribosome
translation regulator activity
acyl−CoA dehydrogenase activity
rRNA binding
flavin adenine dinucleotide binding
ribosome
mitochondrion
mitochondrial small ribosomal subunit
mitochondrial large ribosomal subunit
mitochondrial nucleoid
0 5 10 15 20 25 30
Z Score
M7 black
cellular aldehyde metabolic process
stress−activated MAPK cascade
hexose biosynthetic process
glucose metabolic process
alcohol catabolic process
phosphoprotein binding
protein homodimerization activity
receptor signaling protein activity
catalytic activity
magnesium ion binding
cytosol
cytoplasm
proteasome complex
soluble fraction
0 2 4 6 8
Z Score
M8 pink
protein transport
post−Golgi vesicle−mediated transport
nuclear transport
GTP catabolic process
regulation of defense response to virus by virus
protein transporter activity
GTPase activity
GTP binding
ubiquitin−protein ligase activity
thiolester hydrolase activity
membrane coat
ubiquitin ligase complex
endosome
protein serine/threonine phosphatase complex
endosome membrane
0 2 4 6 8
Z Score
M9 magenta
cholesterol metabolic process
tRNA metabolic process
proteolysis
skeletal system development
gamete generation
hydrolase activity, hydrolyzing O−glycosyl compounds
oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen
serine−type peptidase activity
ligase activity
nuclease activity
Golgi transport complex
microbody part
peroxisome
trans−Golgi network
microsome
0 2 4 6 8 10
Z Score
M10 purple
regulation of Ras protein signal transduction
protein modification process
induction of apoptosis by extracellular signals
nerve growth factor receptor signaling pathway
regulation of cell development
protein serine/threonine kinase activity
guanyl−nucleotide exchange factor activity
transferase activity, transferring hexosyl groups
oxidoreductase activity, acting on paired donors, with incorporation or reduction of molecular oxygen
GTPase activator activity
ATP binding
actin filament
cell projection
cell projection part
early endosome
cytoplasm
0 1 2 3 4 5 6
Z Score
M11 greenyellow
establishment or maintenance of apical/basal cell polarity
leukocyte cell−cell adhesion
cell−matrix adhesion
cell−substrate junction assembly
cell projection assembly
actin binding
integrin binding
zinc ion binding
calcium ion binding
cytoskeleton
cell−substrate junction
cytoplasm
ruffle
basolateral plasma membrane
0 2 4 6 8 10
Z Score

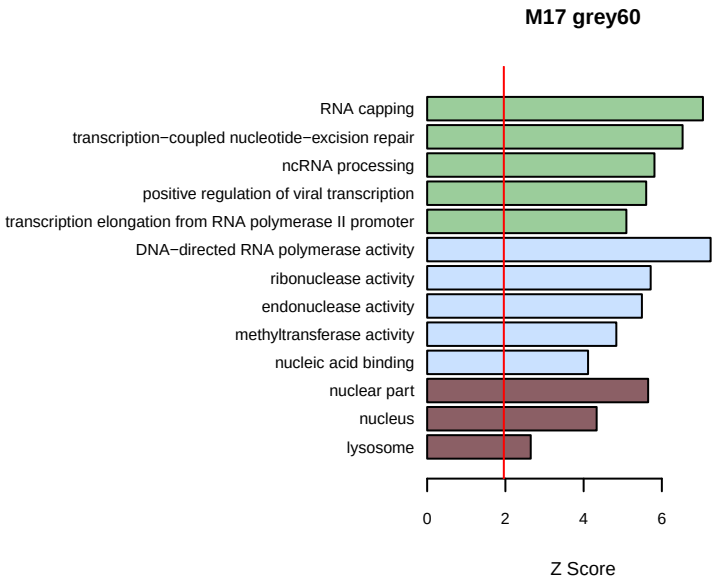

M12 tan
regulation of protein complex disassembly
muscle contraction
regulation of cytoskeleton organization
response to mechanical stimulus
actin filament organization
cytoskeletal protein binding
structural constituent of muscle
calmodulin binding
anion transmembrane transporter activity
protein domain specific binding
adherens junction
cytoskeleton
plasma membrane
cell−substrate junction
cytoplasm
0
2
4
6
8
Z Score

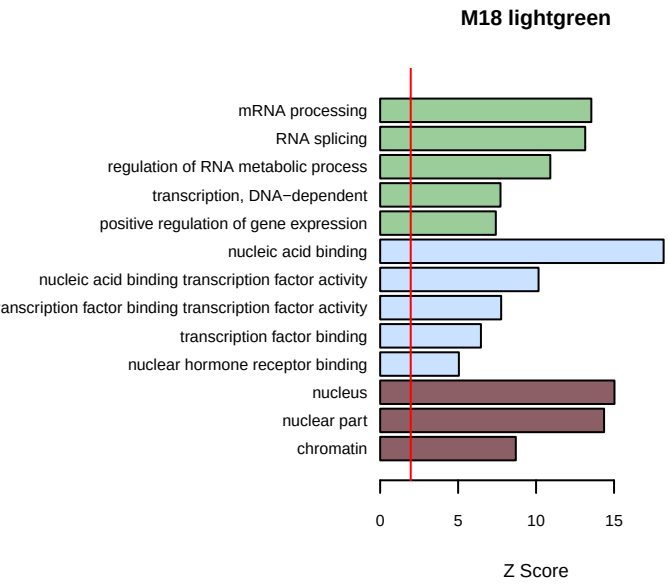

M13 salmon
nuclear mRNA splicing, via spliceosome
termination of RNA polymerase II transcription
protein−DNA complex subunit organization
gene expression
mRNA transport
nucleic acid binding
ATP−dependent helicase activity
chromatin binding
nucleic acid binding transcription factor activity
DNA−dependent ATPase activity
spliceosomal complex
nucleoplasm
small nuclear ribonucleoprotein complex
nucleus
nuclear body
0
5
10
15
20
25
Z Score

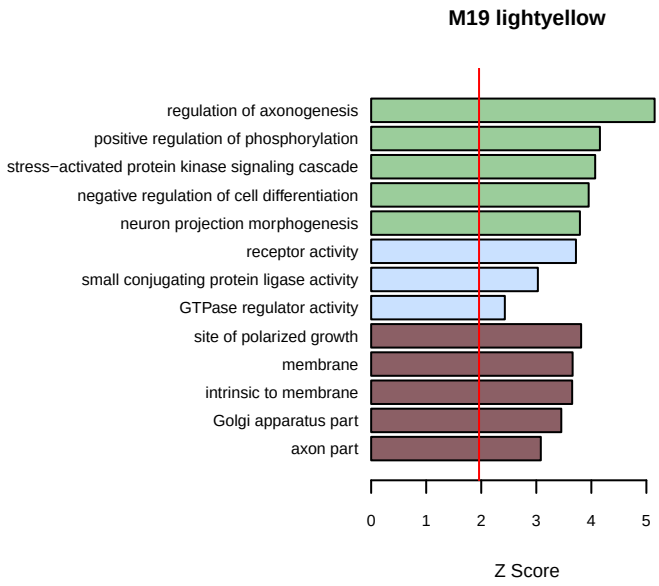

M14 cyan
'de novo' posttranslational protein folding
glycolysis
mitosis
G1/S transition of mitotic cell cycle
cellular protein complex assembly
unfolded protein binding
protein phosphatase regulator activity
GTPase activity
purine ribonucleotide binding
phosphatase activity
chaperonin−containing T−complex
prefoldin complex
cytoplasm
cytoskeleton
cytoskeletal part
0
5
10
15
Z Score

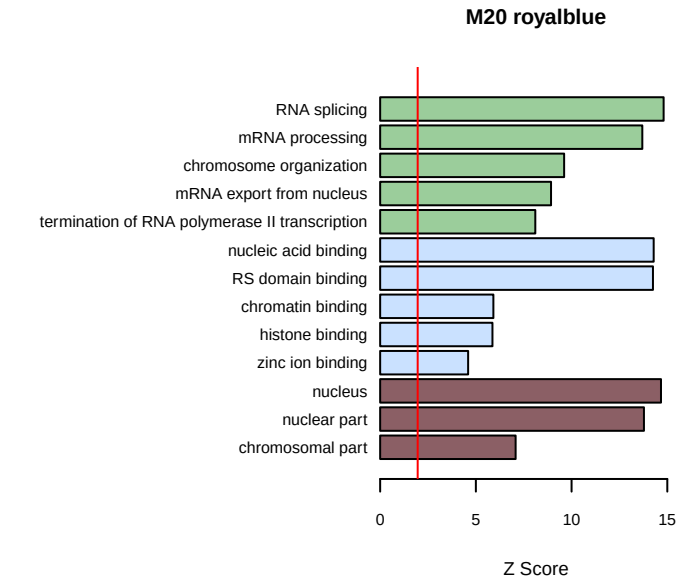

M15 midnightblue
phosphorus metabolic process
negative regulation of protein kinase activity
establishment of localization
hormone metabolic process
regulation of cyclic nucleotide metabolic process
protein kinase regulator activity
protein serine/threonine kinase activity
GTPase activity
enzyme activator activity
purine ribonucleotide binding
cytoplasmic membrane−bounded vesicle
cell projection part
plasma membrane
neuronal cell body
plasma membrane part
0
2
4
6
8
Z Score

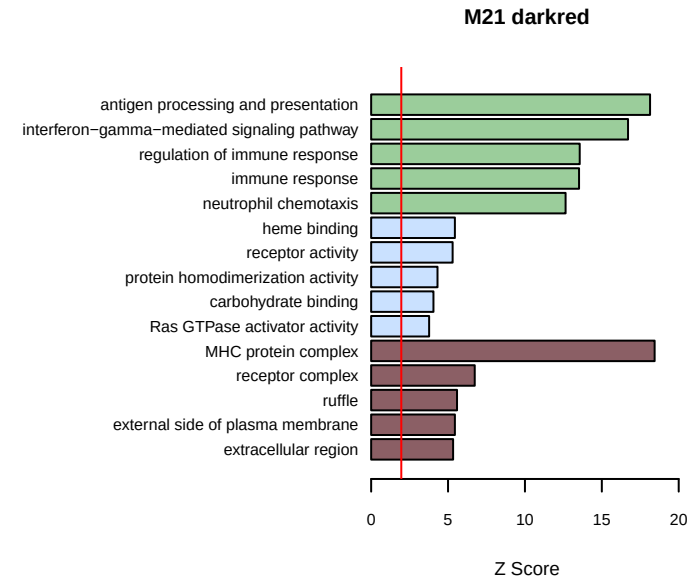

M16 lightcyan
negative regulation of protein complex disassembly
regulation of translation
negative regulation of cytoskeleton organization
establishment of RNA localization
mRNA metabolic process
RNA binding
enzyme inhibitor activity
nucleic acid binding transcription factor activity
nucleus
ribonucleoprotein complex
nuclear membrane
non−membrane−bounded organelle
microtubule
0
1
2
3
4
5
6
Z Score

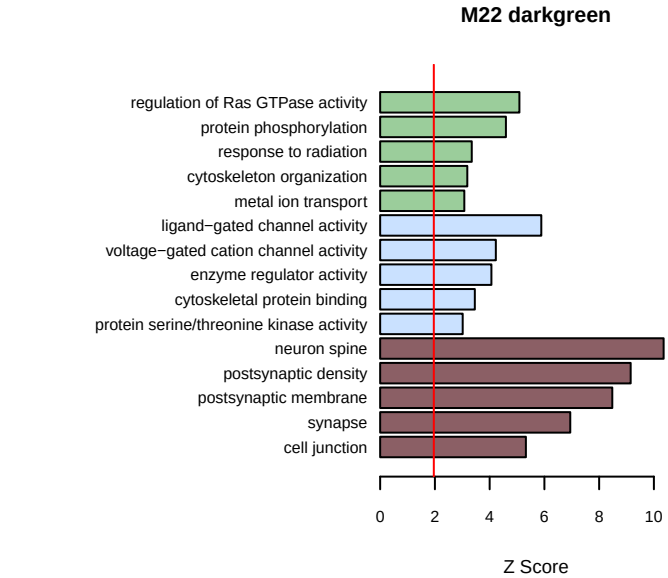

M17 grey60
RNA capping
transcription−coupled nucleotide−excision repair
ncRNA processing
positive regulation of viral transcription
transcription elongation from RNA polymerase II promoter
DNA−directed RNA polymerase activity
ribonuclease activity
endonuclease activity
methyltransferase activity
nucleic acid binding
nuclear part
nucleus
lysosome
0
2
4
6
Z Score

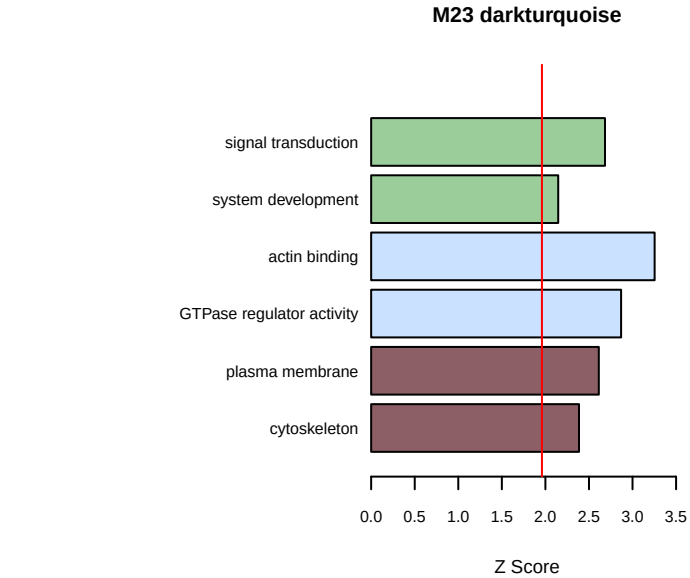

M18 lightgreen
mRNA processing
RNA splicing
regulation of RNA metabolic process
transcription, DNA−dependent
positive regulation of gene expression
nucleic acid binding
nucleic acid binding transcription factor activity
anscription factor binding transcription factor activity
transcription factor binding
nuclear hormone receptor binding
nucleus
nuclear part
chromatin
0
5
10
15
Z Score


M19 lightyellow
regulation of axonogenesis
positive regulation of phosphorylation
stress−activated protein kinase signaling cascade
negative regulation of cell differentiation
neuron projection morphogenesis
receptor activity
small conjugating protein ligase activity
GTPase regulator activity
site of polarized growth
membrane
intrinsic to membrane
Golgi apparatus part
axon part
0
1
2
3
4
5
Z Score

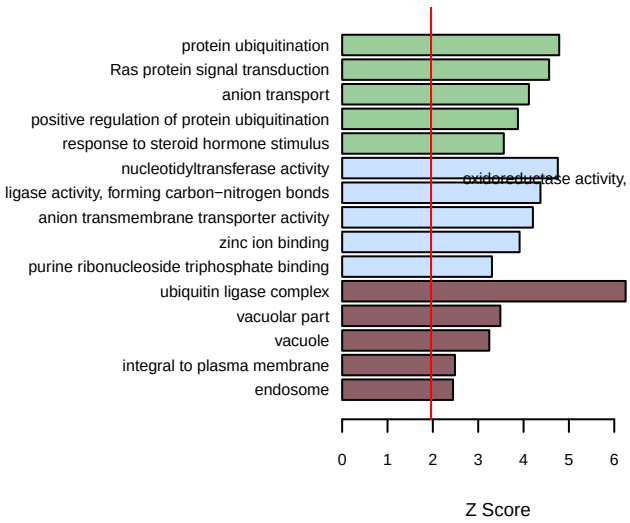

M20 royalblue
RNA splicing
mRNA processing
chromosome organization
mRNA export from nucleus
termination of RNA polymerase II transcription
nucleic acid binding
RS domain binding
chromatin binding
histone binding
zinc ion binding
nucleus
nuclear part
chromosomal part
0
5
10
15
Z Score


M21 darkred
antigen processing and presentation
interferon−gamma−mediated signaling pathway
regulation of immune response
immune response
neutrophil chemotaxis
heme binding
receptor activity
protein homodimerization activity
carbohydrate binding
Ras GTPase activator activity
MHC protein complex
receptor complex
ruffle
external side of plasma membrane
extracellular region
0
5
10
15
20
Z Score

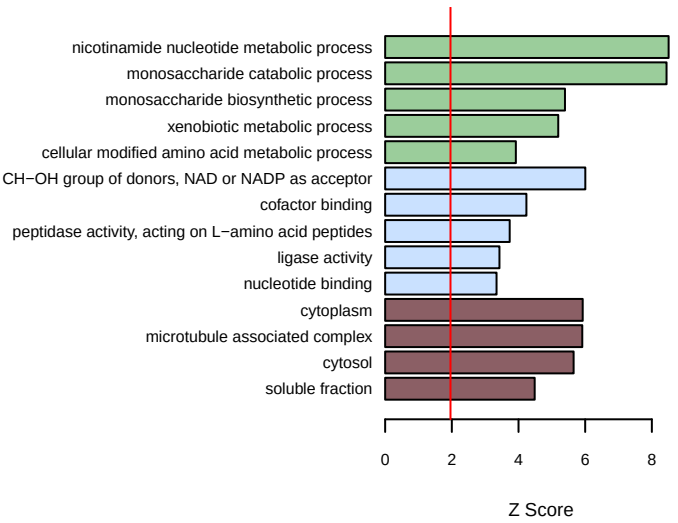

M22 darkgreen
regulation of Ras GTPase activity
protein phosphorylation
response to radiation
cytoskeleton organization
metal ion transport
ligand−gated channel activity
voltage−gated cation channel activity
enzyme regulator activity
cytoskeletal protein binding
protein serine/threonine kinase activity
neuron spine
postsynaptic density
postsynaptic membrane
synapse
cell junction
0
2
4
6
8
10
Z Score


M23 darkturquoise
signal transduction
system development
actin binding
GTPase regulator activity
plasma membrane
cytoskeleton
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
Z Score

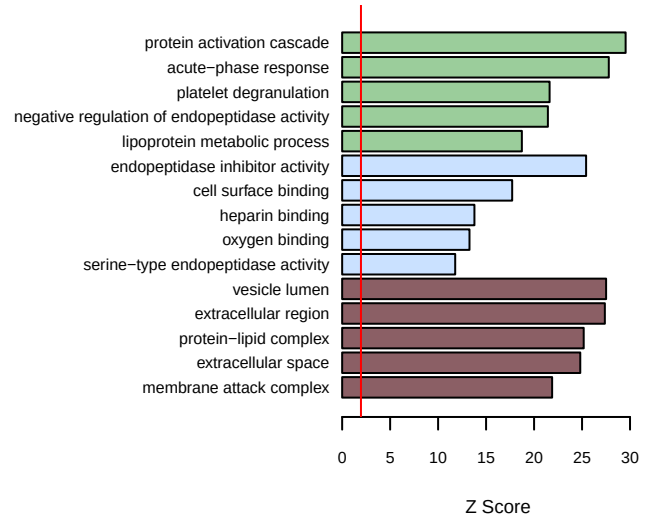
M24 darkgrey



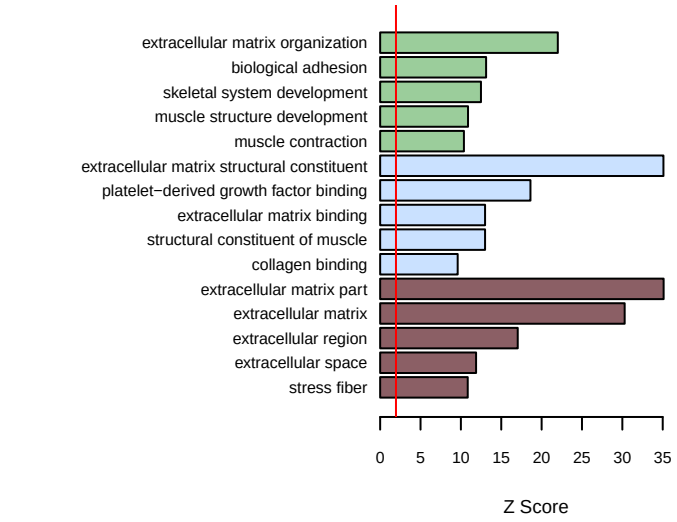
M25 orange



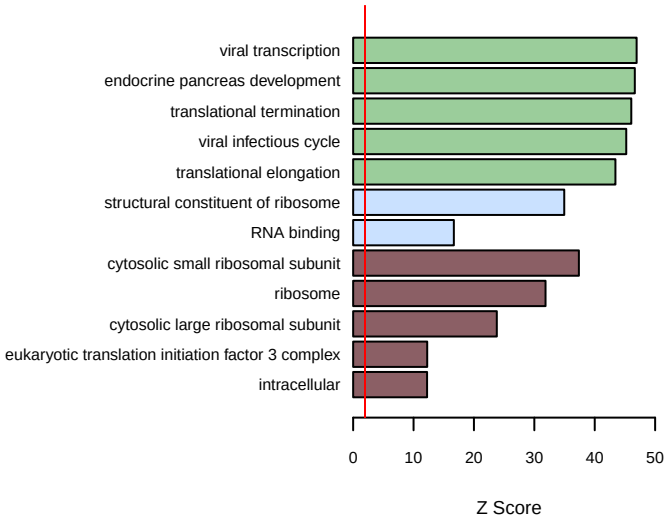
M26 darkorange



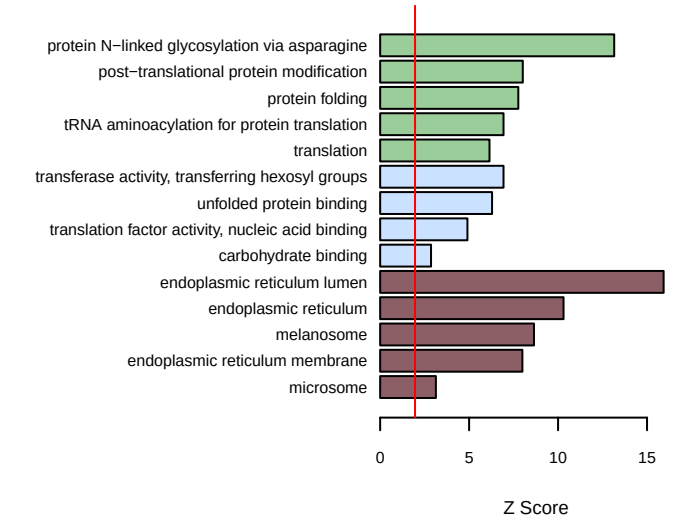
M27 white



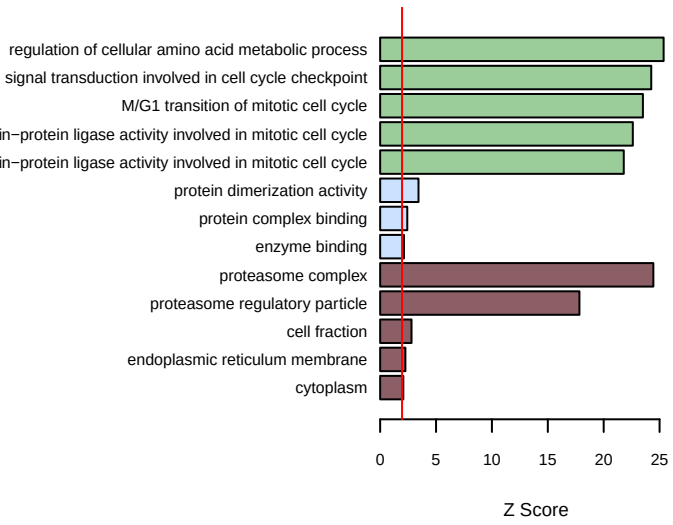
M28 skyblue



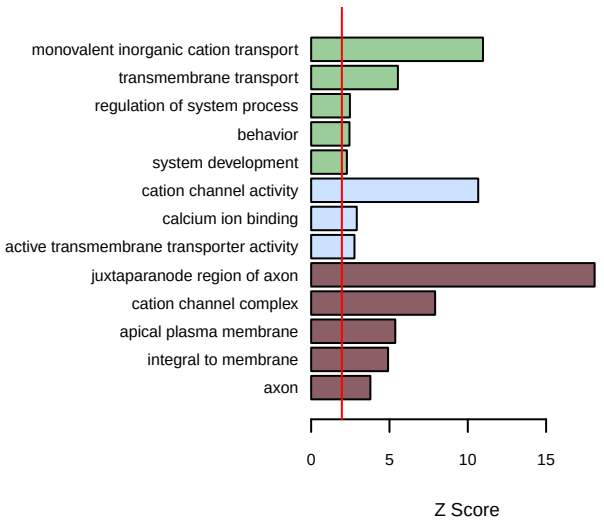
M29 saddlebrown



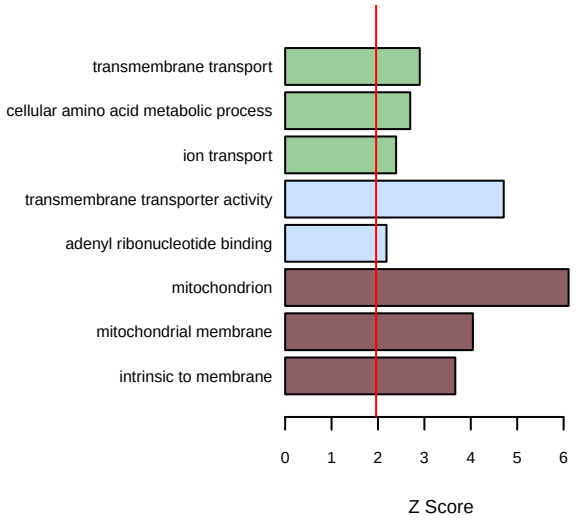
M30 steelblue



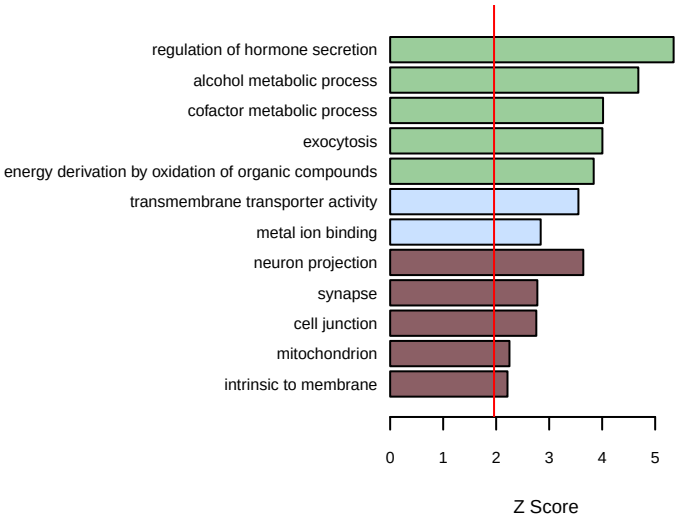
M31 paleturquoise



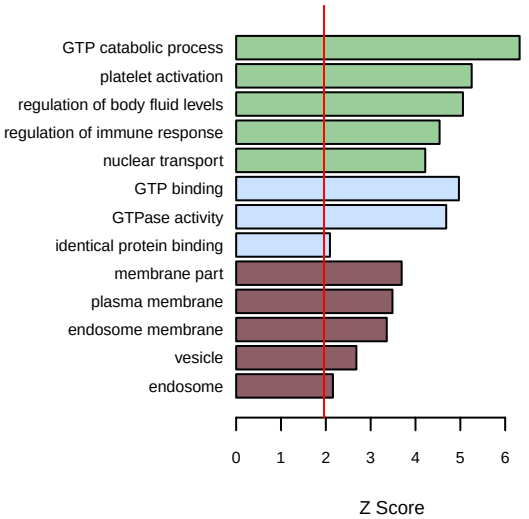
M32 violet



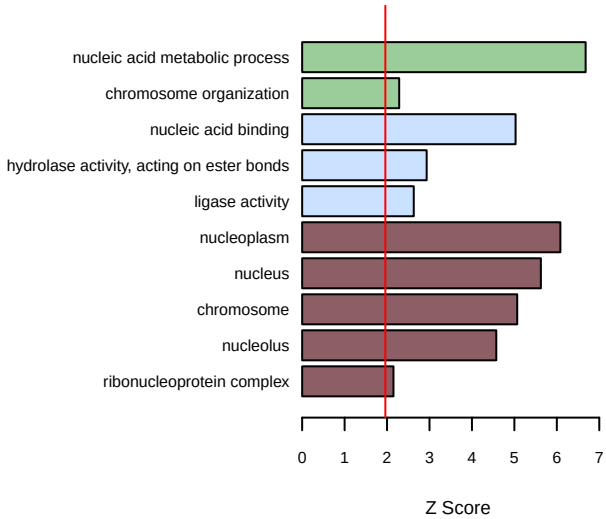
M33 darkolivegreen

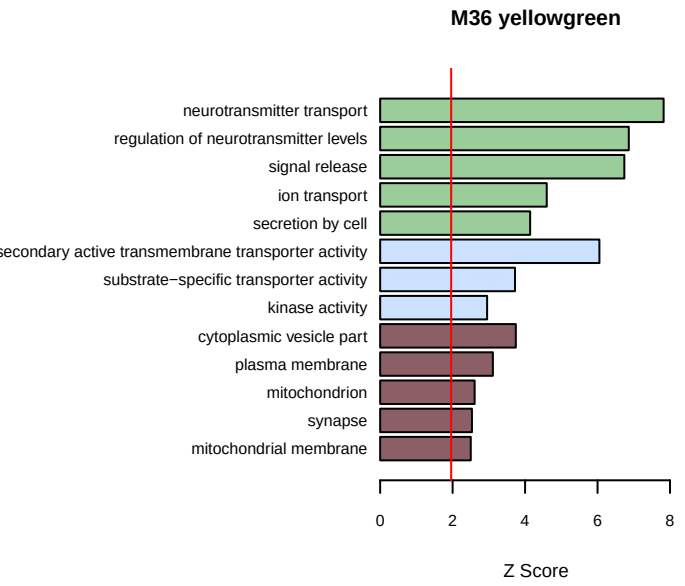


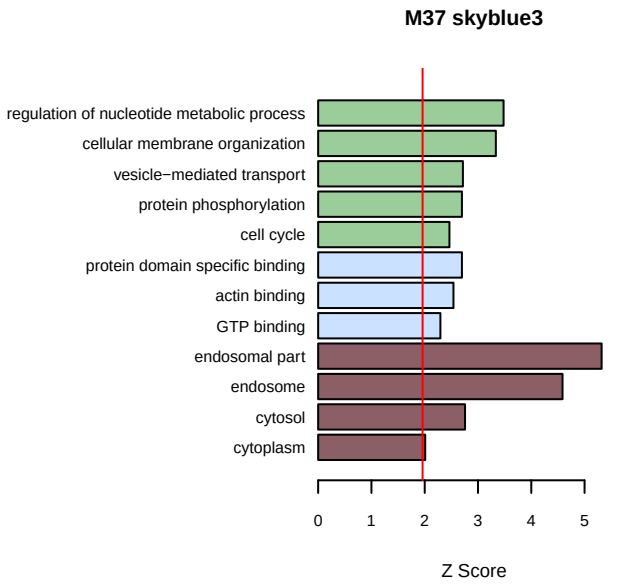
M34 darkmagenta

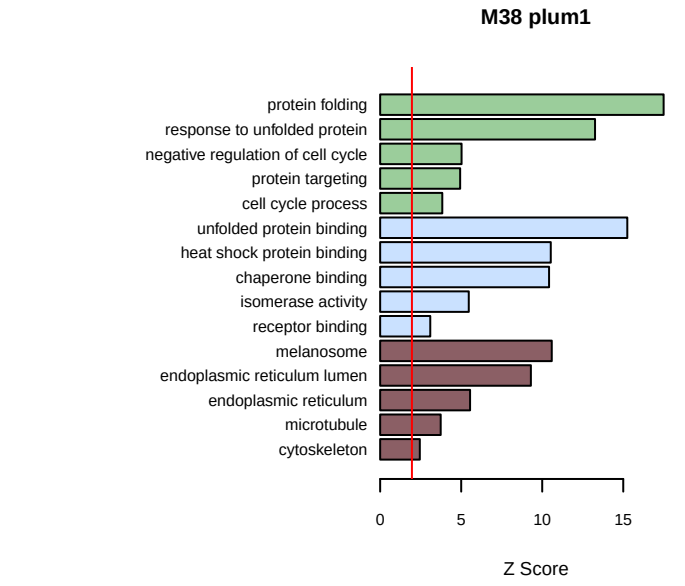


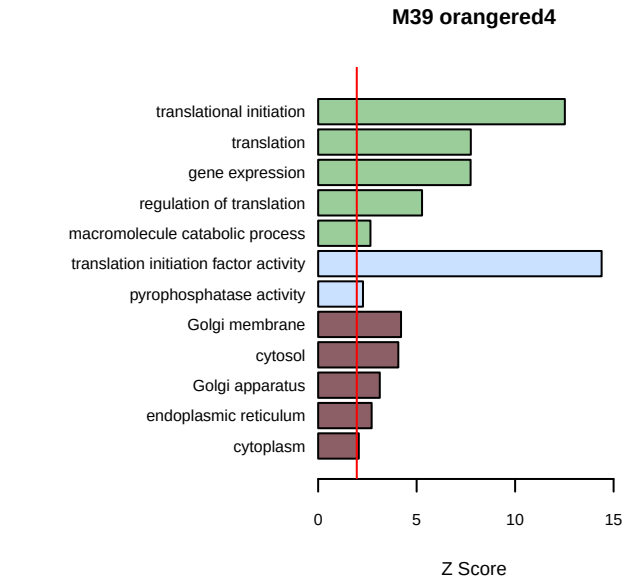
M35 sienna3

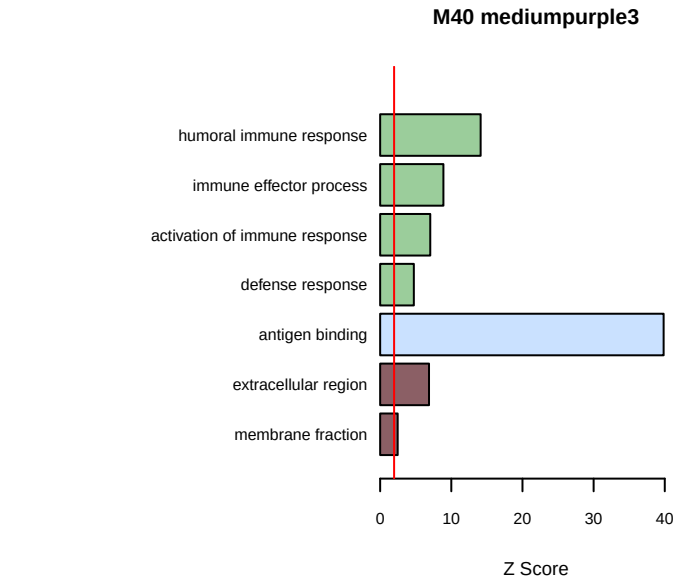


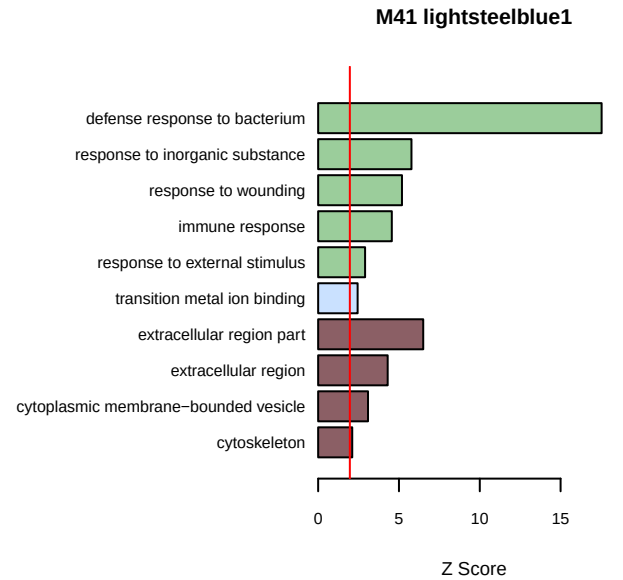

M36 yellowgreen
neurotransmitter transport
regulation of neurotransmitter levels
signal release
ion transport
secretion by cell
secondary active transmembrane transporter activity
substrate−specific transporter activity
kinase activity
cytoplasmic vesicle part
plasma membrane
mitochondrion
synapse
mitochondrial membrane
0
2
4
6
8
Z Score


M37 skyblue3
regulation of nucleotide metabolic process
cellular membrane organization
vesicle−mediated transport
protein phosphorylation
cell cycle
protein domain specific binding
actin binding
GTP binding
endosomal part
endosome
cytosol
cytoplasm
0
1
2
3
4
5
Z Score

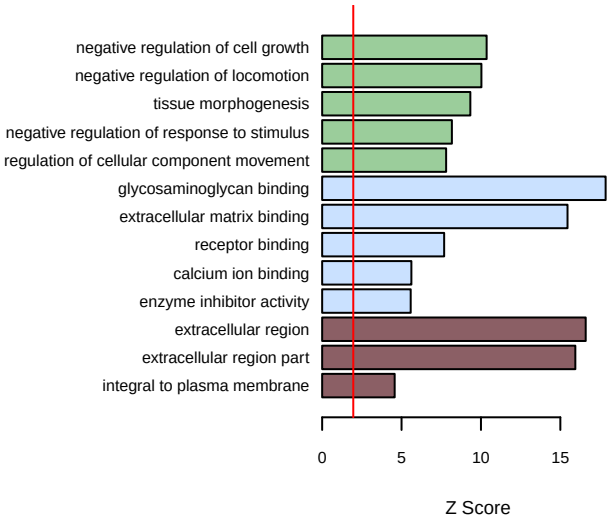

M38 plum1
protein folding
response to unfolded protein
negative regulation of cell cycle
protein targeting
cell cycle process
unfolded protein binding
heat shock protein binding
chaperone binding
isomerase activity
receptor binding
melanosome
endoplasmic reticulum lumen
endoplasmic reticulum
microtubule
cytoskeleton
0
5
10
15
Z Score


M39 orangered4
translational initiation
translation
gene expression
regulation of translation
macromolecule catabolic process
translation initiation factor activity
pyrophosphatase activity
Golgi membrane
cytosol
Golgi apparatus
endoplasmic reticulum
cytoplasm
0
5
10
15
Z Score

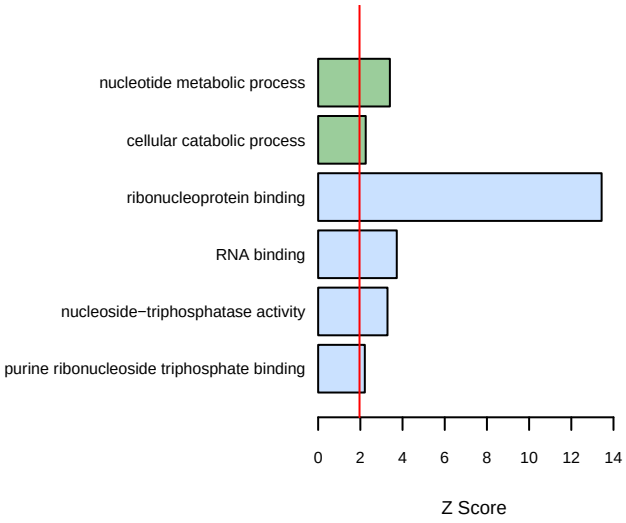

M40 mediumpurple3
humoral immune response
immune effector process
activation of immune response
defense response
antigen binding
extracellular region
membrane fraction
0
10
20
30
40
Z Score


M41 lightsteelblue1
defense response to bacterium
response to inorganic substance
response to wounding
immune response
response to external stimulus
transition metal ion binding
extracellular region part
extracellular region
cytoplasmic membrane−bounded vesicle
cytoskeleton
0
5
10
15
Z Score

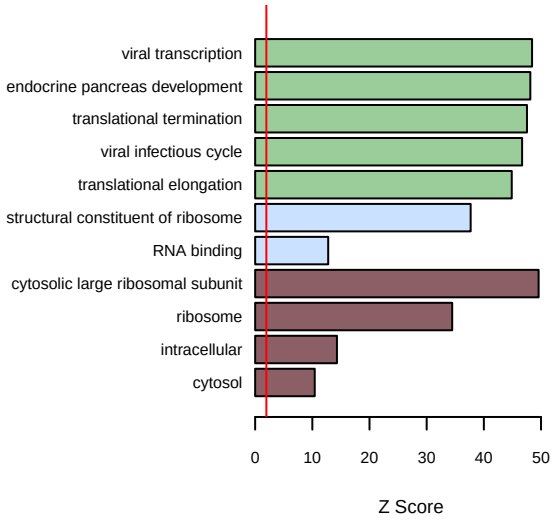
M42 lightcyan1

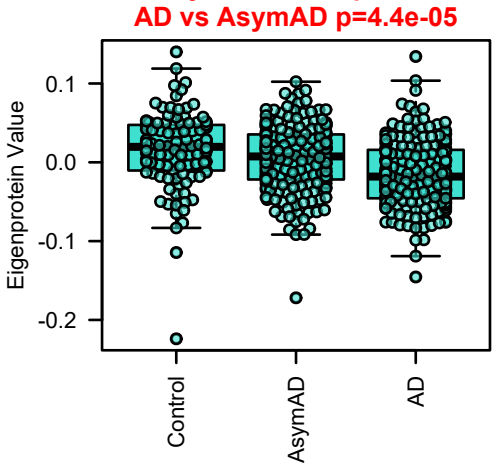


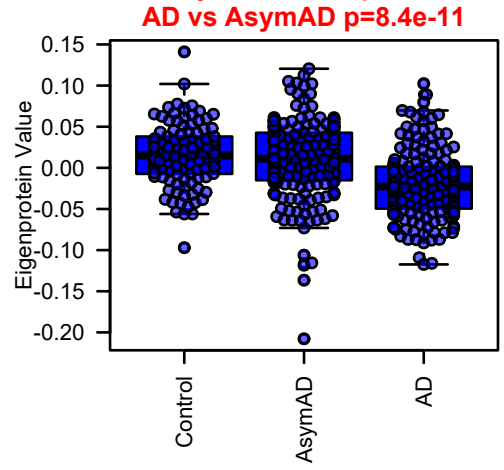
M43 ivory

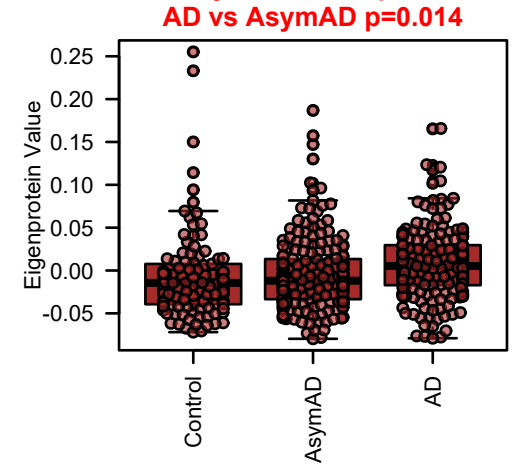


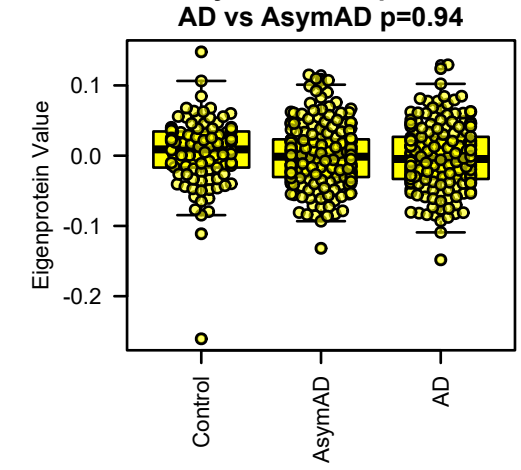
M44 floralwhite

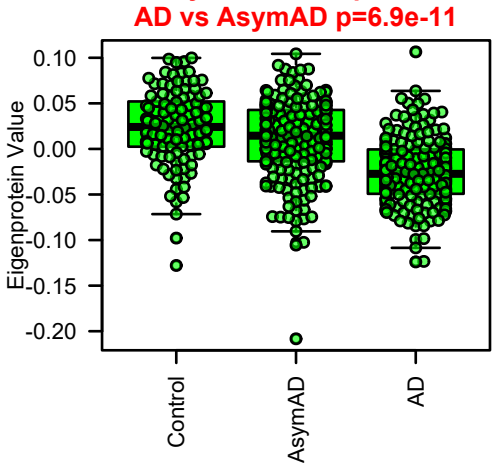


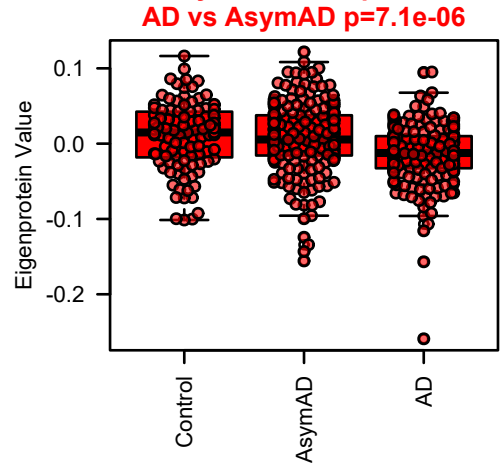

M1 turquoise
AD vs CT Tukey p=8.2e-08
AsymAD vs CT p=0.11
AD vs AsymAD p=4.4e-05
Eigenprotein Value
Control
AsymAD
AD

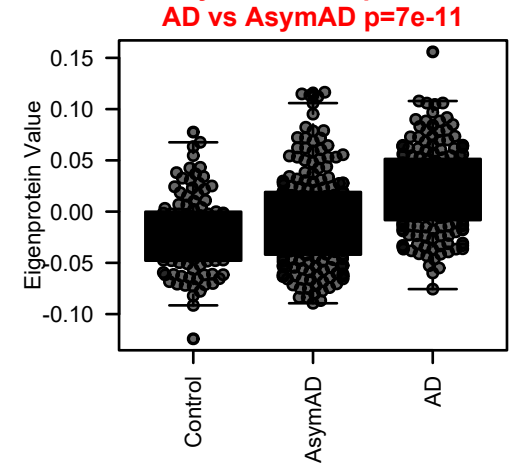

M2 blue
AD vs CT Tukey p=1.1e-10
AsymAD vs CT p=0.57
AD vs AsymAD p=8.4e-11
Eigenprotein Value
Control
AsymAD
AD

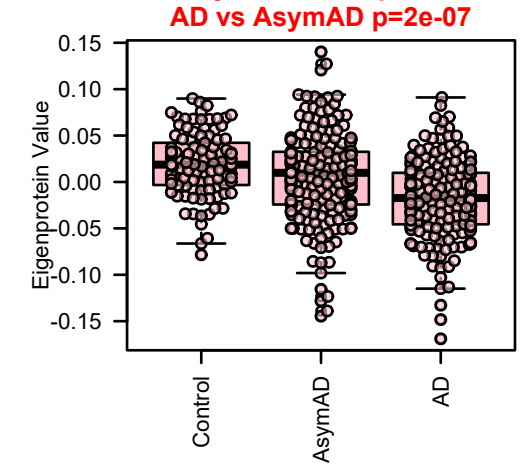

M3 brown
AD vs CT Tukey p=0.015
AsymAD vs CT p=0.9
AD vs AsymAD p=0.014
Eigenprotein Value
Control
AsymAD
AD

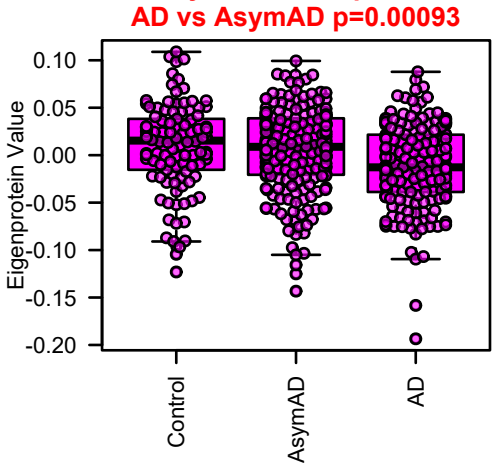

M4 yellow
AD vs CT Tukey p=0.42
AsymAD vs CT p=0.58
AD vs AsymAD p=0.94
Eigenprotein Value
Control
AsymAD
AD

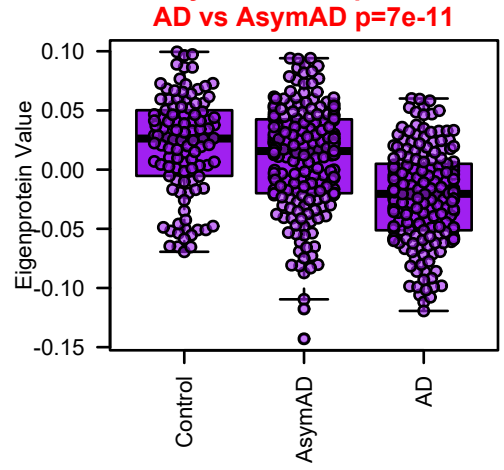

M5 green
AD vs CT Tukey p=6.9e-11
AsymAD vs CT p=0.03
AD vs AsymAD p=6.9e-11
Eigenprotein Value
Control
AsymAD
AD

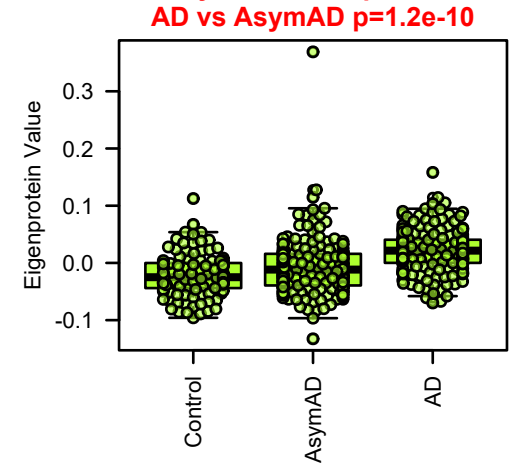

M6 red
AD vs CT Tukey p=3.7e-05
AsymAD vs CT p=0.91
AD vs AsymAD p=7.1e-06
Eigenprotein Value
Control
AsymAD
AD

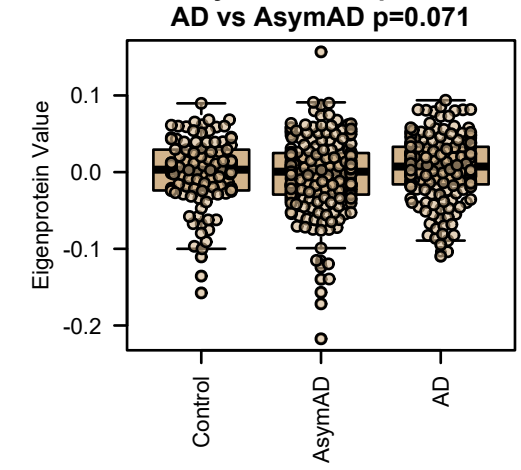

M7 black
AD vs CT Tukey p=6.9e-11
AsymAD vs CT p=0.083
AD vs AsymAD p=7e-11
Eigenprotein Value
Control
AsymAD
AD

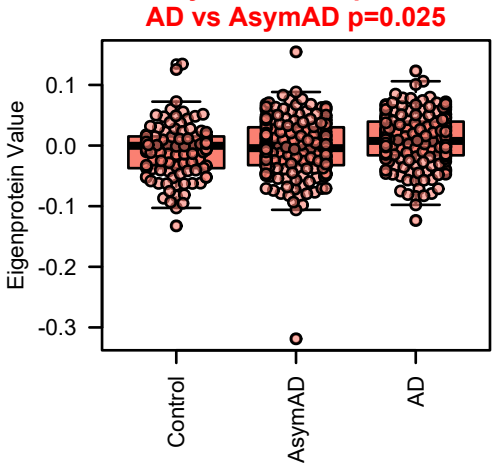

M8 pink
AD vs CT Tukey p=9.7e-11
AsymAD vs CT p=0.04
AD vs AsymAD p=2e-07
Eigenprotein Value
Control
AsymAD
AD

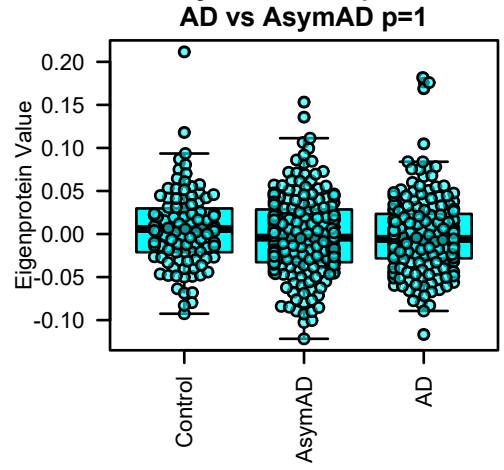

M9 magenta
AD vs CT Tukey p=0.00057
AsymAD vs CT p=0.75
AD vs AsymAD p=0.00093
Eigenprotein Value
Control
AsymAD
AD

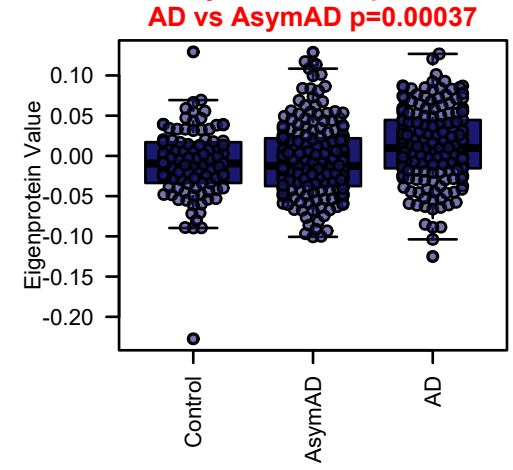

M10 purple
AD vs CT Tukey p=6.9e-11
AsymAD vs CT p=0.079
AD vs AsymAD p=7e-11
Eigenprotein Value
Control
AsymAD
AD

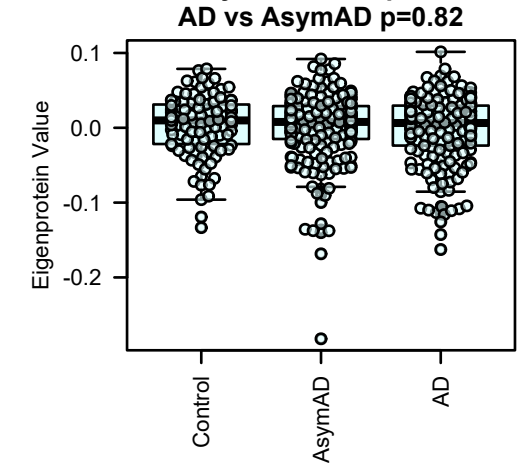

M11 greenyellow
AD vs CT Tukey p=6.9e-11
AsymAD vs CT p=0.034
AD vs AsymAD p=1.2e-10
Eigenprotein Value
Control
AsymAD
AD

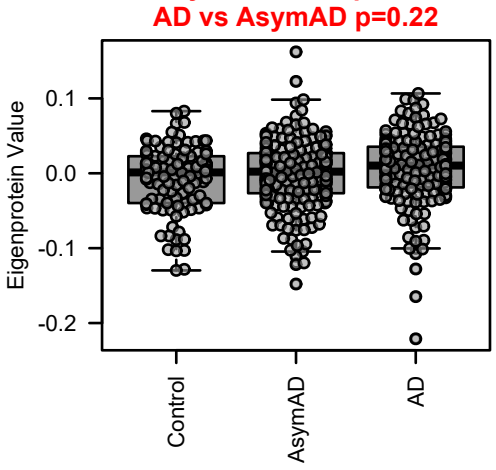

M12 tan
AD vs CT Tukey p=0.4
AsymAD vs CT p=0.84
AD vs AsymAD p=0.071
Eigenprotein Value
Control
AsymAD
AD

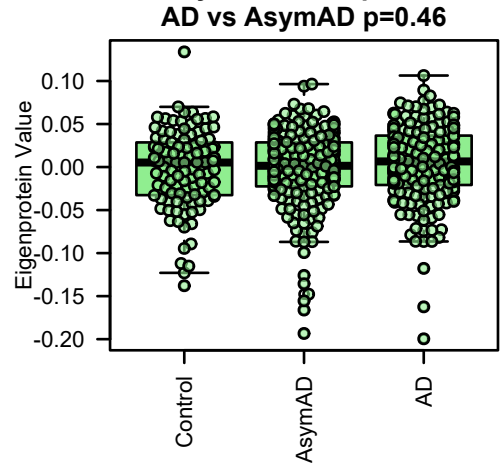

M13 salmon
AD vs CT Tukey p=0.0061
AsymAD vs CT p=0.64
AD vs AsymAD p=0.025
Eigenprotein Value
Control
AsymAD
AD

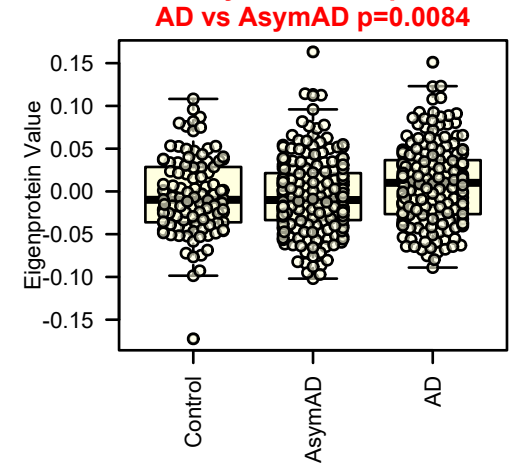

M14 cyan
AD vs CT Tukey p=0.34
AsymAD vs CT p=0.33
AD vs AsymAD p=1
Eigenprotein Value
Control
AsymAD
AD

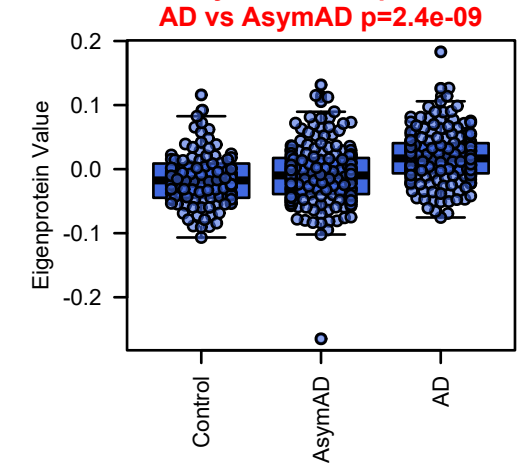

M15 midnightblue
AD vs CT Tukey p=0.00023
AsymAD vs CT p=0.73
AD vs AsymAD p=0.00037
Eigenprotein Value
Control
AsymAD
AD

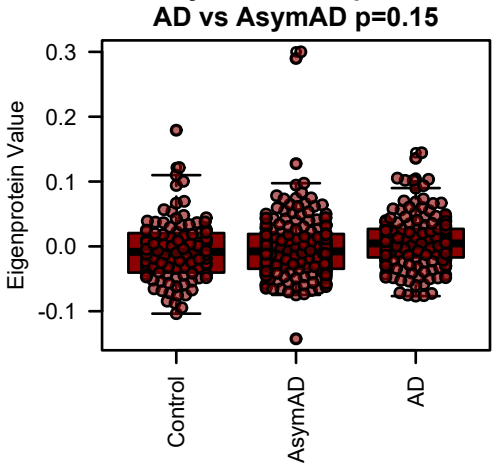

M16 lightcyan
AD vs CT Tukey p=0.62
AsymAD vs CT p=0.9
AD vs AsymAD p=0.82
Eigenprotein Value
Control
AsymAD
AD

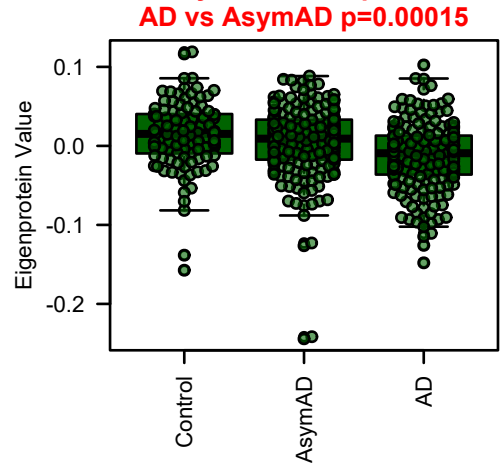

M17 grey60
AD vs CT Tukey p=0.042
AsymAD vs CT p=0.55
AD vs AsymAD p=0.22
Eigenprotein Value
Control
AsymAD
AD

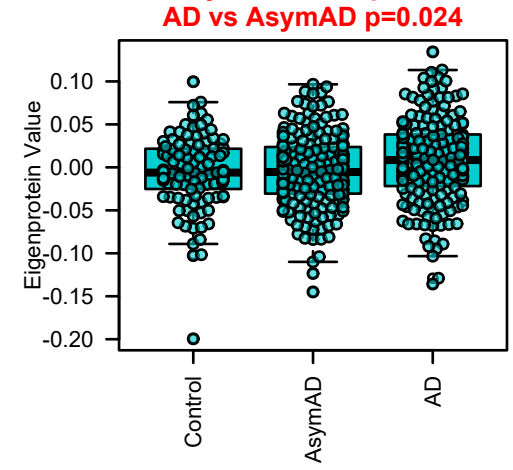

M18 lightgreen
AD vs CT Tukey p=0.43
AsymAD vs CT p=0.97
AD vs AsymAD p=0.46
Eigenprotein Value
Control
AsymAD
AD

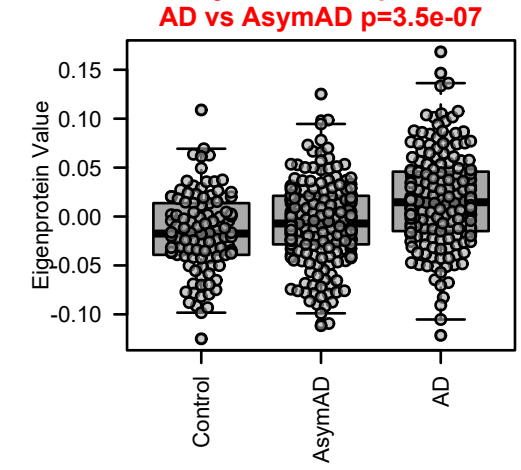

M19 lightyellow
AD vs CT Tukey p=0.033
AsymAD vs CT p=1
AD vs AsymAD p=0.0084
Eigenprotein Value
Control
AsymAD
AD

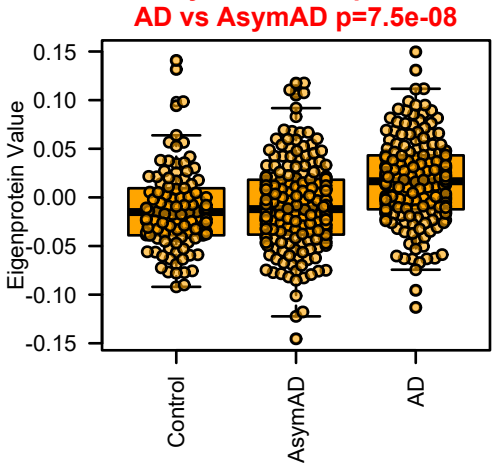

M20 royalblue
AD vs CT Tukey p=4.3e-10
AsymAD vs CT p=0.37
AD vs AsymAD p=2.4e-09
Eigenprotein Value
Control
AsymAD
AD

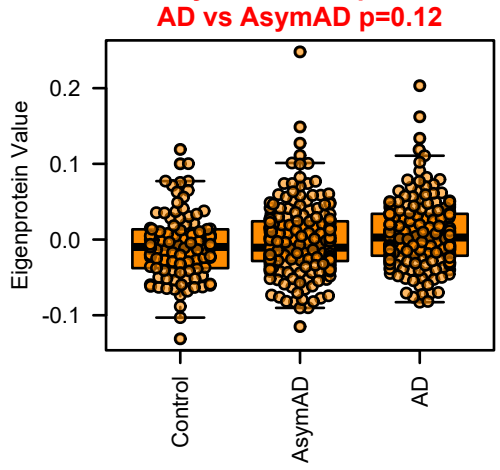

M21 darkred
AD vs CT Tukey p=0.063
AsymAD vs CT p=0.76
AD vs AsymAD p=0.15
Eigenprotein Value
Control
AsymAD
AD

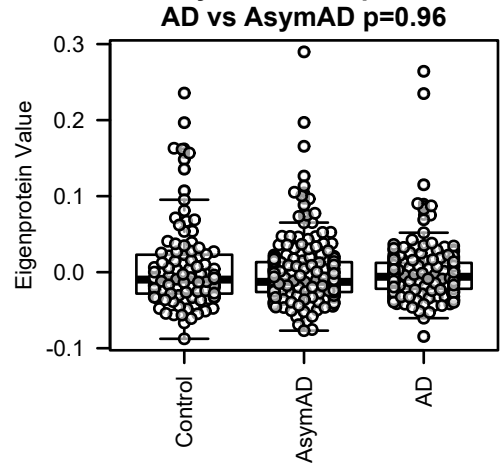

M22 darkgreen
AD vs CT Tukey p=2e-06
AsymAD vs CT p=0.23
AD vs AsymAD p=0.00015
Eigenprotein Value
Control
AsymAD
AD

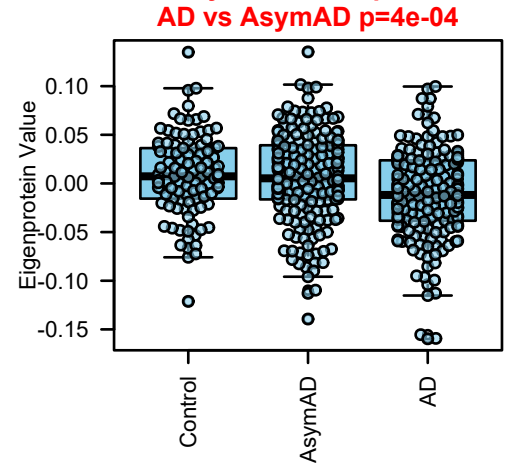

M23 darkturquoise
AD vs CT Tukey p=0.033
AsymAD vs CT p=0.95
AD vs AsymAD p=0.024
Eigenprotein Value
Control
AsymAD
AD

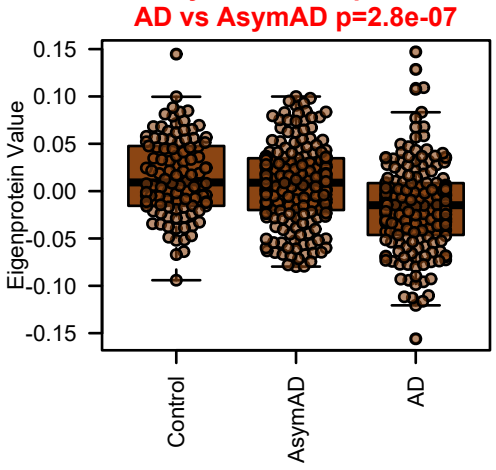

M24 darkgrey
AD vs CT Tukey p=1.7e-09
AsymAD vs CT p=0.15
AD vs AsymAD p=3.5e-07
Eigenprotein Value
Control
AsymAD
AD

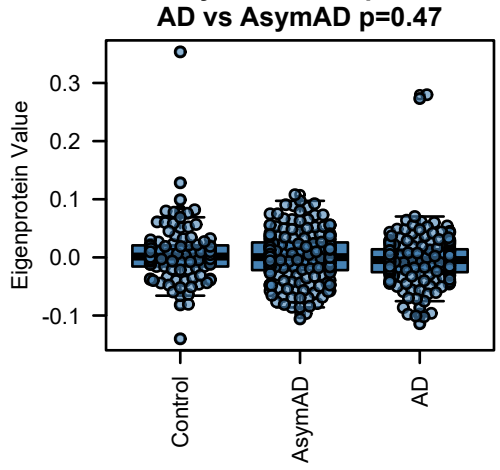

M25 orange
AD vs CT Tukey p=2.6e-07
AsymAD vs CT p=0.77
AD vs AsymAD p=7.5e-08
Eigenprotein Value
Control
AsymAD
AD

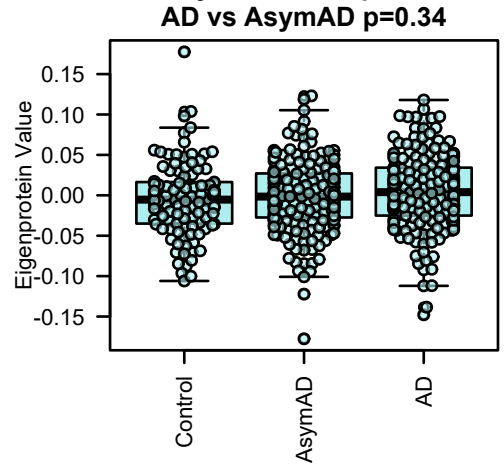

M26 darkorange
AD vs CT Tukey p=0.015
AsymAD vs CT p=0.48
AD vs AsymAD p=0.12
Eigenprotein Value
Control
AsymAD
AD

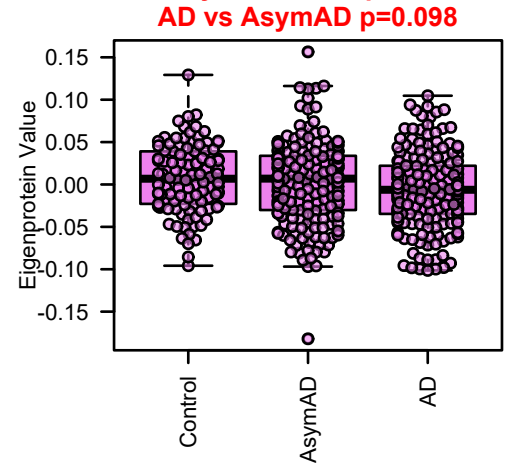

M27 white
AD vs CT Tukey p=0.48
AsymAD vs CT p=0.34
AD vs AsymAD p=0.96
Eigenprotein Value
Control
AsymAD
AD

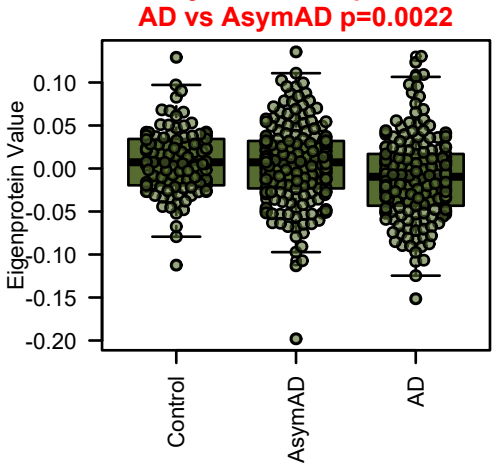

M28 skyblue
AD vs CT Tukey p=0.00086
AsymAD vs CT p=0.9
AD vs AsymAD p=4e-04
Eigenprotein Value
Control
AsymAD
AD

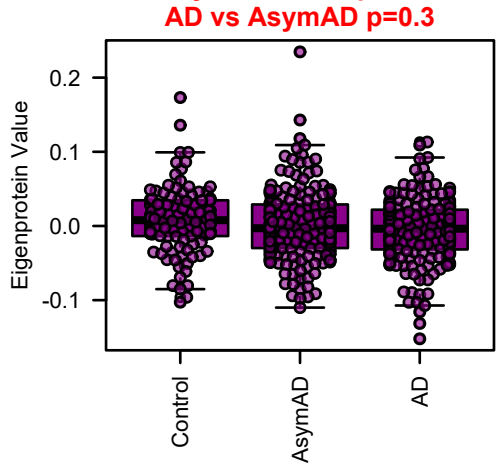

M29 saddlebrown
AD vs CT Tukey p=1e-08
AsymAD vs CT p=0.29
AD vs AsymAD p=2.8e-07
Eigenprotein Value
Control
AsymAD
AD

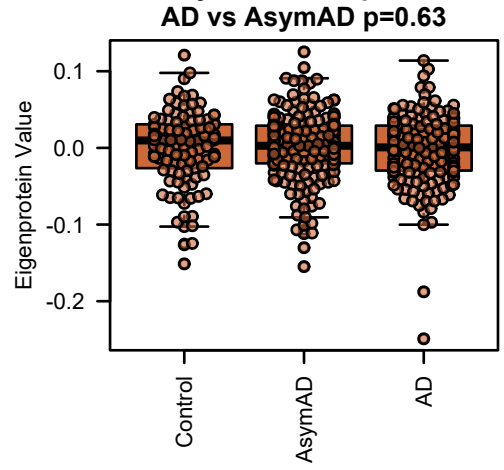

M30 steelblue
AD vs CT Tukey p=0.18
AsymAD vs CT p=0.7
AD vs AsymAD p=0.47
Eigenprotein Value
Control
AsymAD
AD

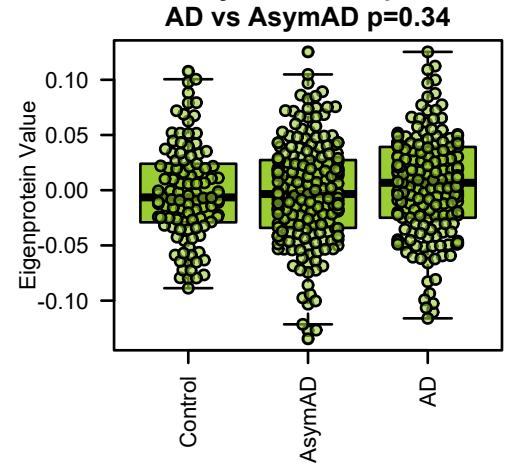

M31 paleturquoise
AD vs CT Tukey p=0.19
AsymAD vs CT p=0.82
AD vs AsymAD p=0.34
Eigenprotein Value
Control
AsymAD
AD

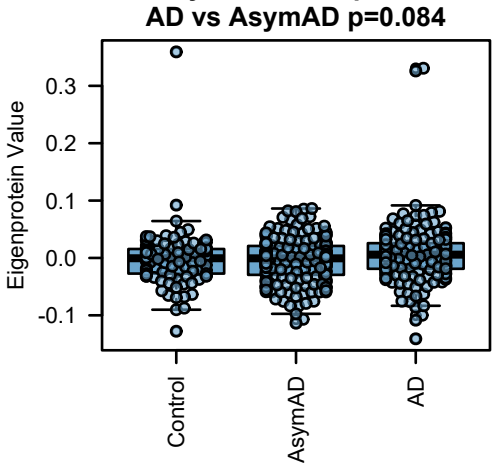

M32 violet
AD vs CT Tukey p=0.033
AsymAD vs CT p=0.71
AD vs AsymAD p=0.098
Eigenprotein Value
Control
AsymAD
AD

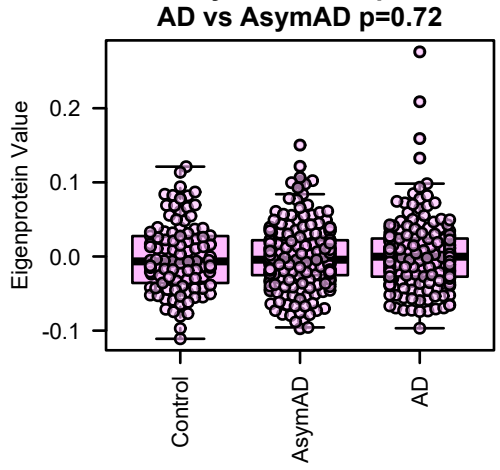

M33 darkolivegreen
AD vs CT Tukey p=0.0021
AsymAD vs CT p=0.84
AD vs AsymAD p=0.0022
Eigenprotein Value
Control
AsymAD
AD

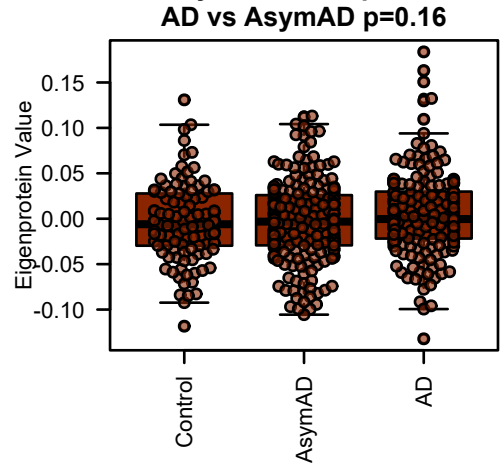

M34 darkmagenta
AD vs CT Tukey p=0.043
AsymAD vs CT p=0.46
AD vs AsymAD p=0.3
Eigenprotein Value
Control
AsymAD
AD

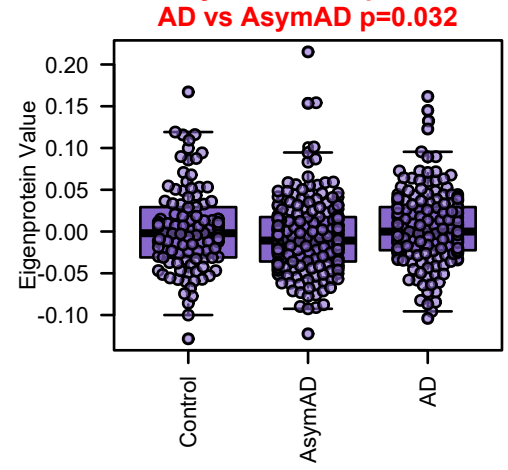

M35 sienna3
AD vs CT Tukey p=0.98
AsymAD vs CT p=0.84
AD vs AsymAD p=0.63
Eigenprotein Value
Control
AsymAD
AD

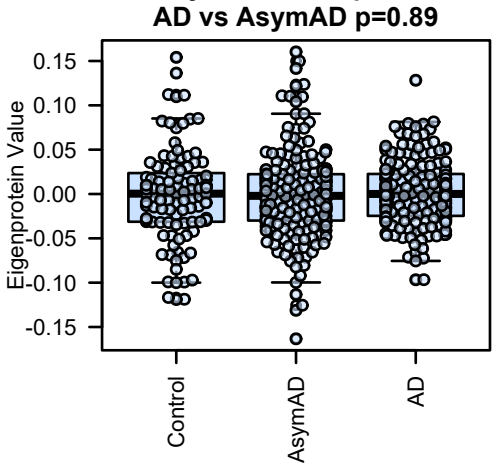

M36 yellowgreen
AD vs CT Tukey p=0.48
AsymAD vs CT p=1
AD vs AsymAD p=0.34
Eigenprotein Value
Control
AsymAD
AD

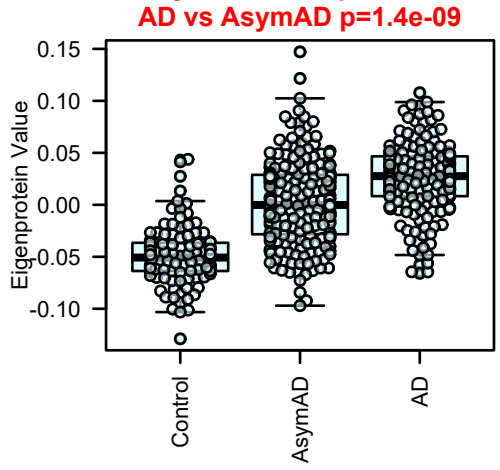

M37 skyblue3
AD vs CT Tukey p=0.33
AsymAD vs CT p=0.93
AD vs AsymAD p=0.084
Eigenprotein Value
Control
AsymAD
AD

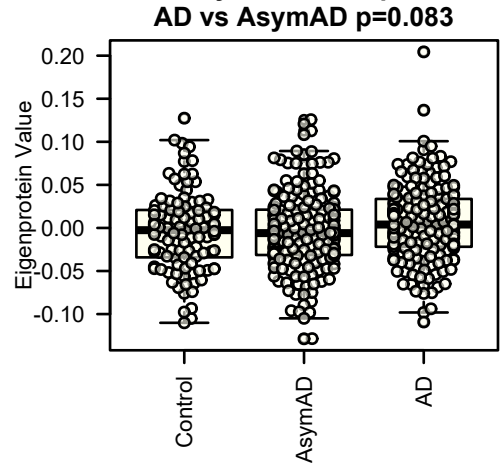

M38 plum1
AD vs CT Tukey p=0.81
AsymAD vs CT p=1
AD vs AsymAD p=0.72
Eigenprotein Value
Control
AsymAD
AD

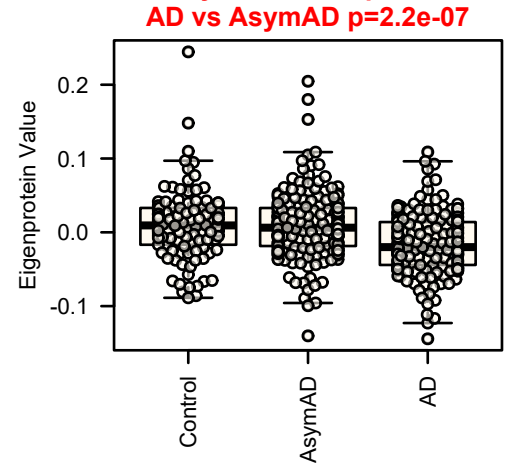

M39 orangered4
AD vs CT Tukey p=0.19
AsymAD vs CT p=0.97
AD vs AsymAD p=0.16
Eigenprotein Value
Control
AsymAD
AD

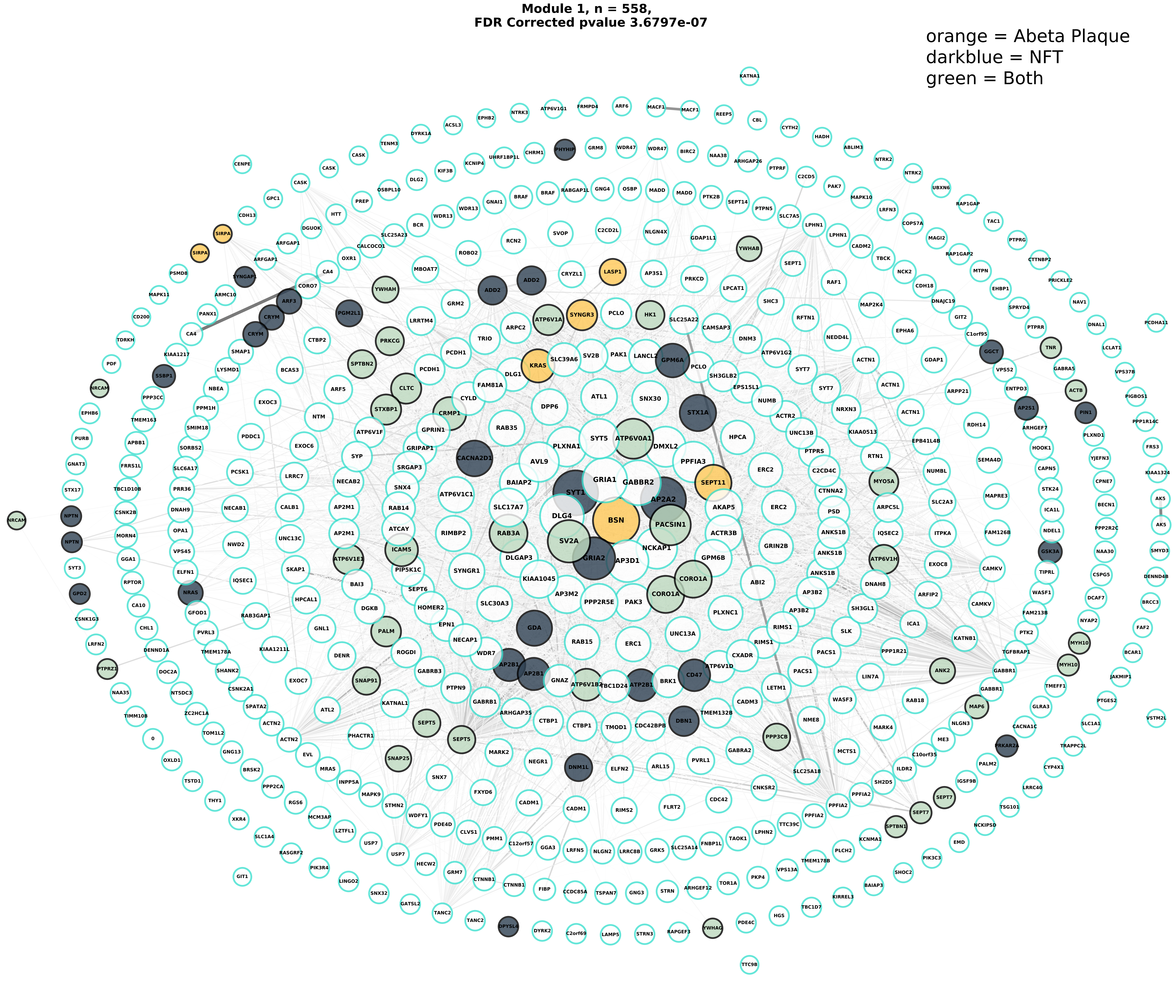

M40 mediumpurple3
AD vs CT Tukey p=0.86
AsymAD vs CT p=0.24
AD vs AsymAD p=0.032
Eigenprotein Value
Control
AsymAD
AD


M41 lightsteelblue1
AD vs CT Tukey p=0.84
AsymAD vs CT p=0.98
AD vs AsymAD p=0.89
Eigenprotein Value
Control
AsymAD
AD


M42 lightcyan1
AD vs CT Tukey p=6.9e-11
AsymAD vs CT p=6.9e-11
AD vs AsymAD p=1.4e-09
Eigenprotein Value
Control
AsymAD
AD


M43 ivory
AD vs CT Tukey p=0.16
AsymAD vs CT p=1
AD vs AsymAD p=0.083
Eigenprotein Value
Control
AsymAD
AD


M44 floralwhite
AD vs CT Tukey p=7.8e-06
AsymAD vs CT p=0.98
AD vs AsymAD p=2.2e-07
Eigenprotein Value
Control
AsymAD
AD


Module 1, n = 558,
FDR Corrected pvalue 3.6797e-07
orange = Abeta Plaque
darkblue = NFT
green = Both
KATNA1
CENPE
CASK
CASK
CASK
TENM3
DYRK1A
ACSL3
EPHB2
NTRK3
ATP6V1G1
FRMPD4
ARF6
MACF1
MACF1
REEP5
CBL
CYTH2
HADH
ABLIM3
NTRK2
NTRK2
UBXN6
RAP1GAP
TAC1
PTPRG
CTTNBP2
PRICKLE2
NAV1
DNAL1
PCDHA11
LCLAT1
VPS37B
PIGBOS1
PPP1R14C
FRS3
KIAA1324
AK5
AK5
SMYD3
DENND4B
BRCC3
FAF2
BCAR1
JAKMIP1
PTGES2
VSTM2L
SLC1A1
TRAPPC2L
CYP4X1
LRRC40
TSG101
NCKIPSD
EMD
PIK3C3
SHOC2
BAIAP3
KIRREL3
TBC1D7
HGS
TTC9B
PDE4C
YWHAG
RAPGEF3
STRN3
LAMP5
C2orf69
DYRK2
DPYSL4
TANC2
TANC2
GATSL2
SNX32
LINGO2
PIK3R4
RASGRF2
GIT1
SLC1A4
XKR4
THY1
TSTD1
OXLD1
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TIMM10B
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GPD2
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STX17
GNAT3
PURB
EPHB6
NRCAM
PDF
TDRKH
CD200
MAPK11
PSMD8
SIRPA
SIRPA
CDH13
GPC1
PHYHIP
CHRM1
UHRF1BP1L
KCNIP4
KIF3B
DLG2
OSBPL10
PREP
HTT
DGUOK
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SYNGAP1
ARMC10
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CA4
CORO7
ARF3
CRYM
CRYM
KIAA1217
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MORN4
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GRM7
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CPNE7
YJEFN3
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PIN1
ACTB
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SPRYD4
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MAGI2
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PAK7
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BIRC2
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WDR47
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MADD
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LPHN1
CADM2
TBCK
NCK2
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DNAJC19
GIT2
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ENTPD3
AP2S1
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NDEL1
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CRMP1
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HK1
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GABBR2
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ERC2
ERC2
PPFIA3
AVL9
PLXNA1
SYT5
ATP6V0A1
DMXL2
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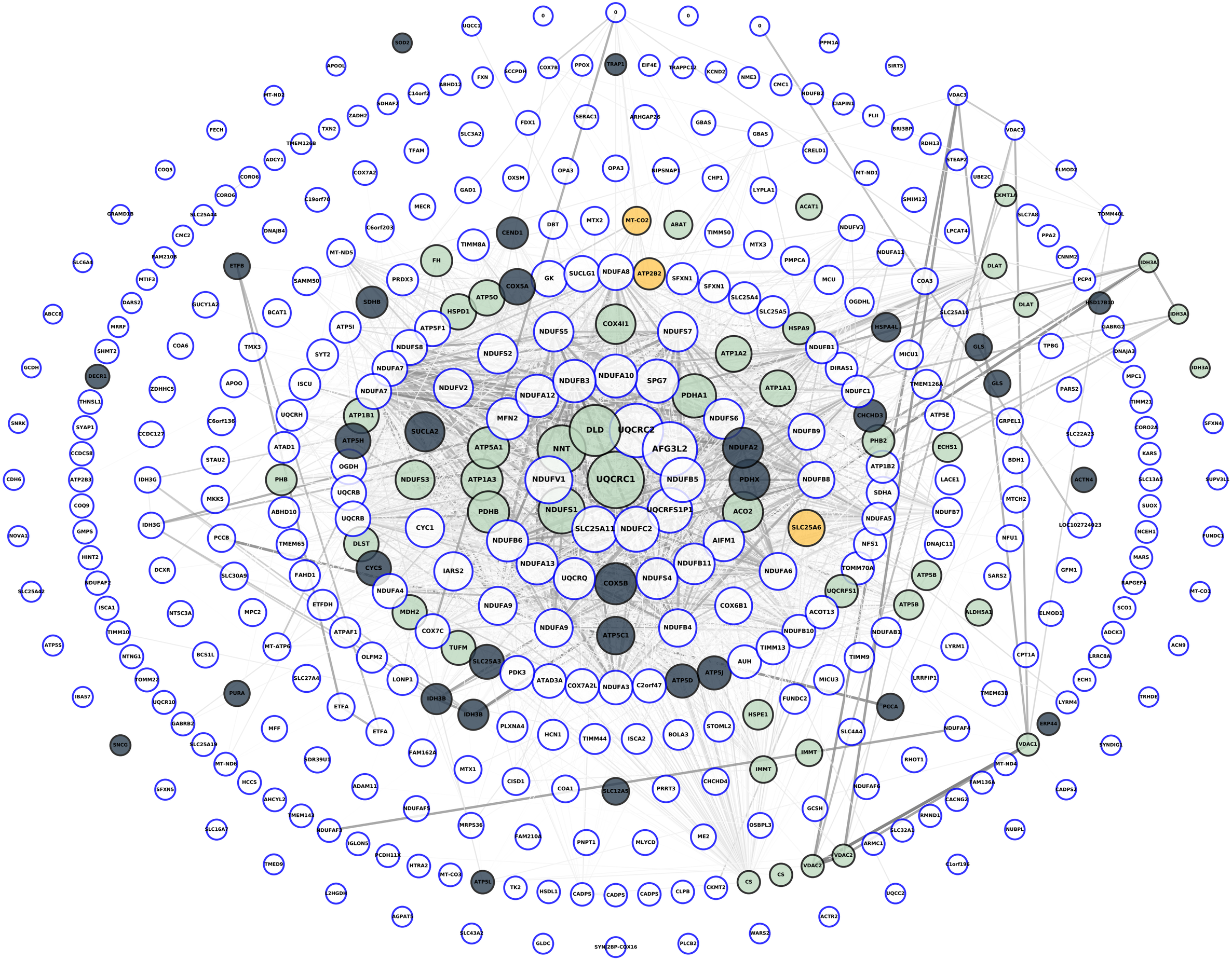
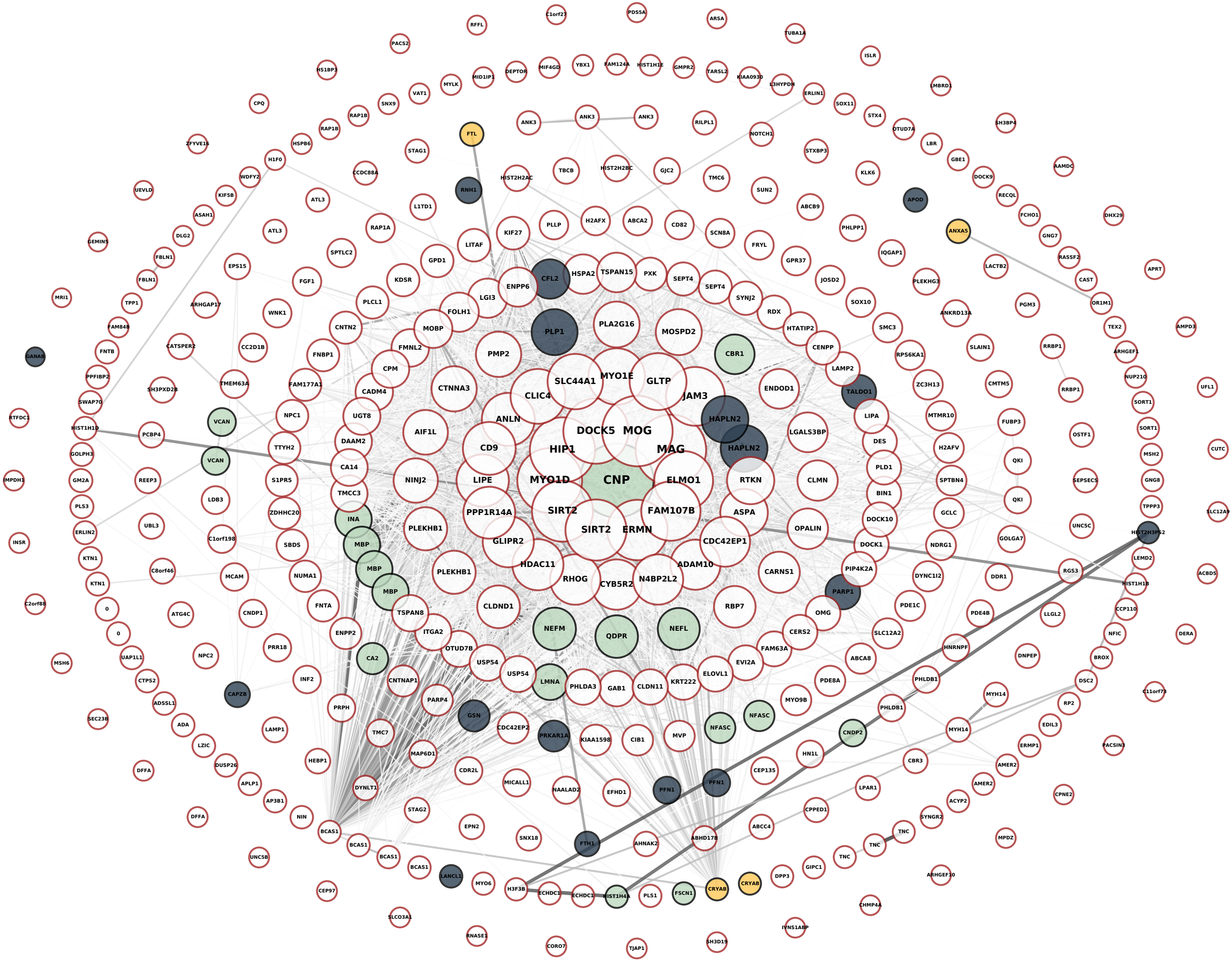
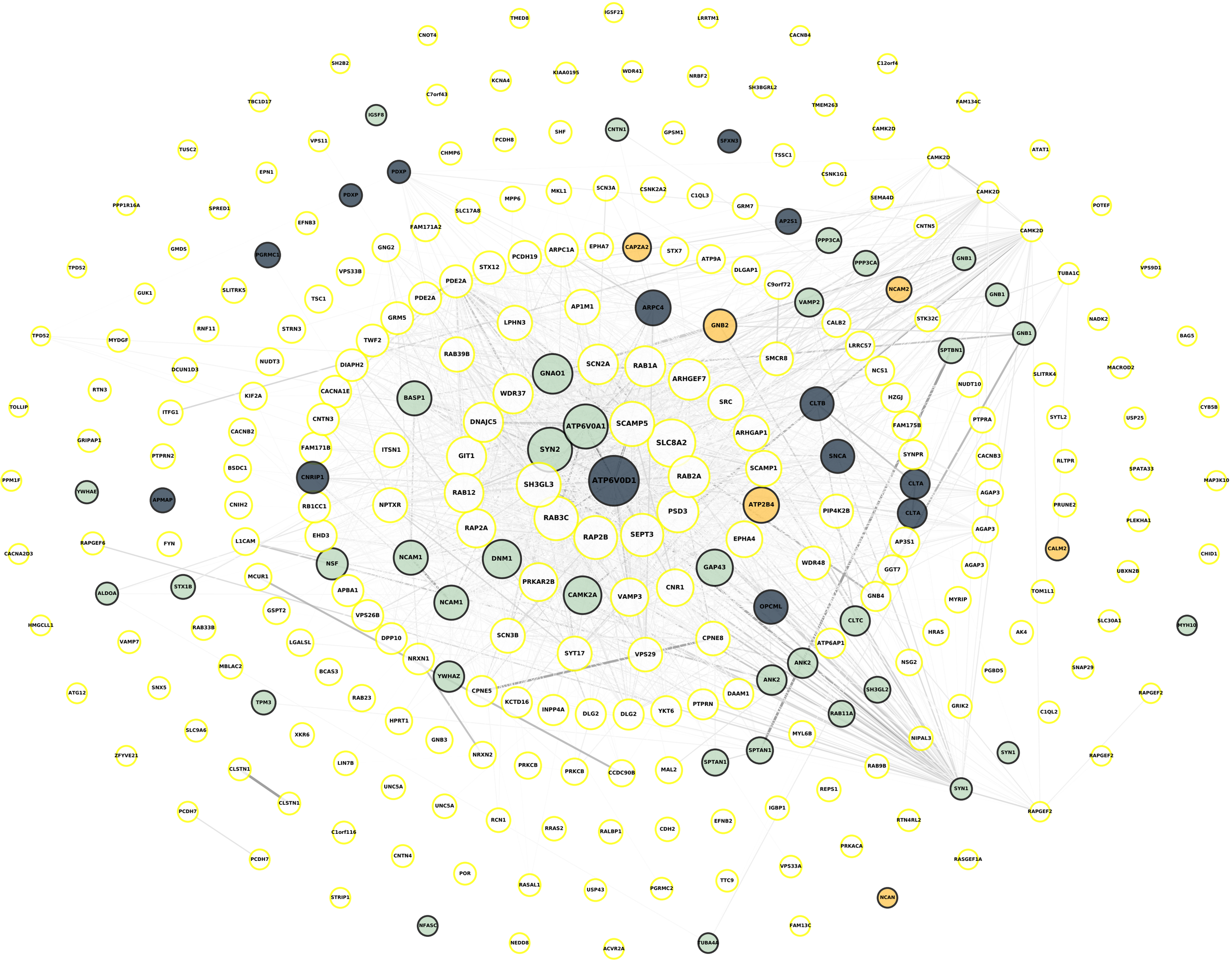
Module 2, n = 403,
FDR Corrected pvalue 1.6412e-14



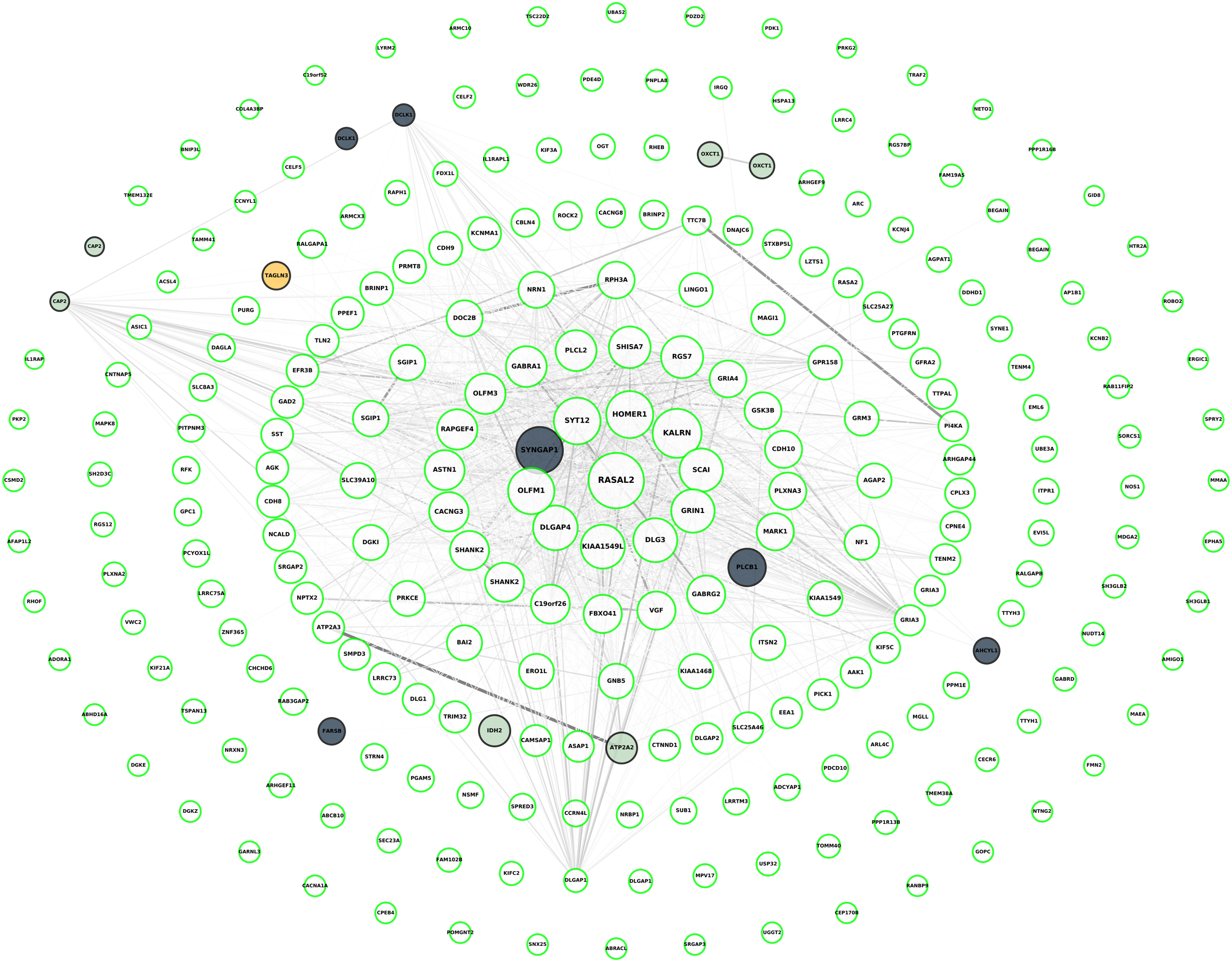
Module 3, n = 398,
FDR Corrected pvalue 0.18123



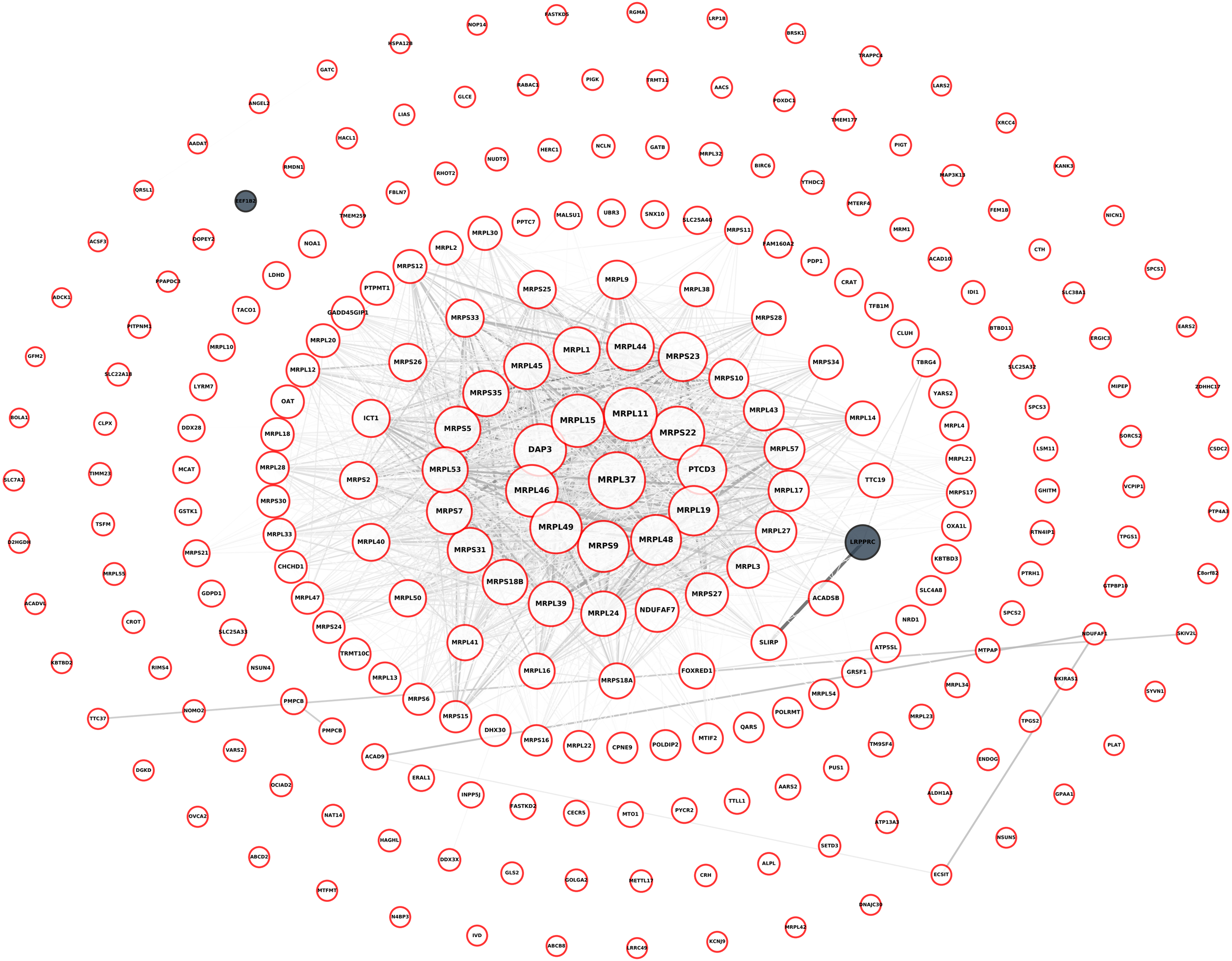
Module 4, n = 291,
FDR Corrected pvalue 1.6684e-07



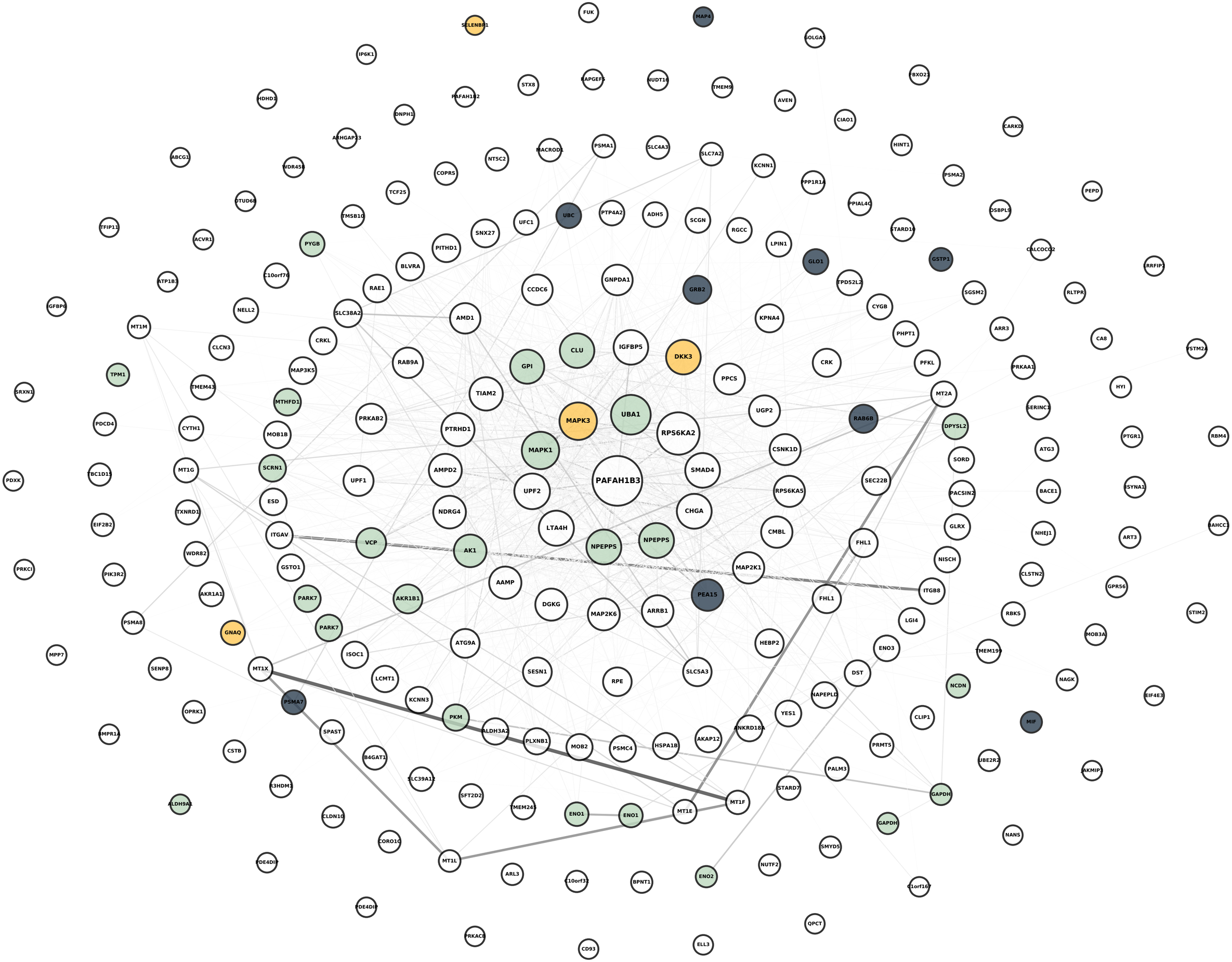
Module 5, n = 249,
FDR Corrected pvalue 1



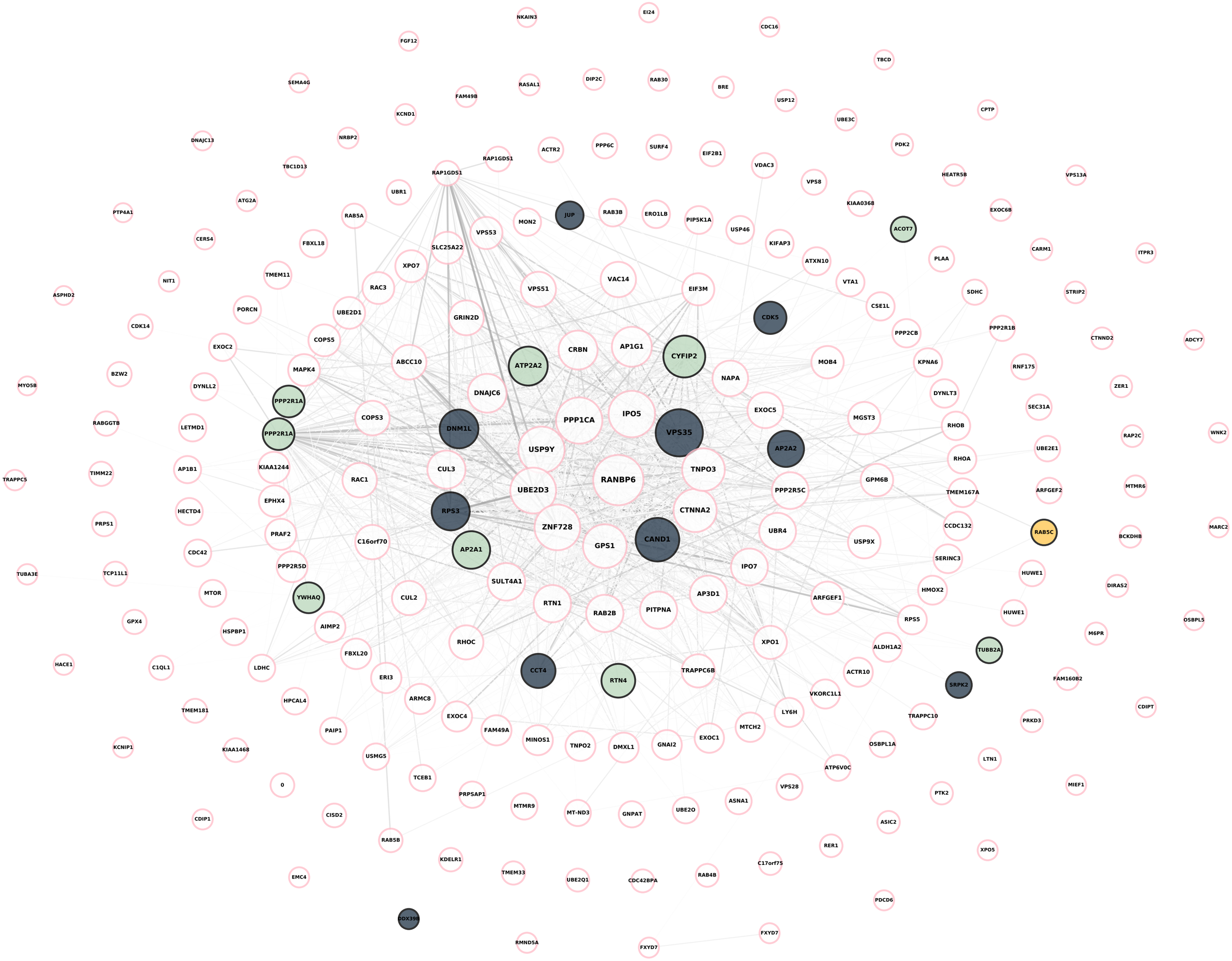
Module 6, n = 248,
FDR Corrected pvalue 1



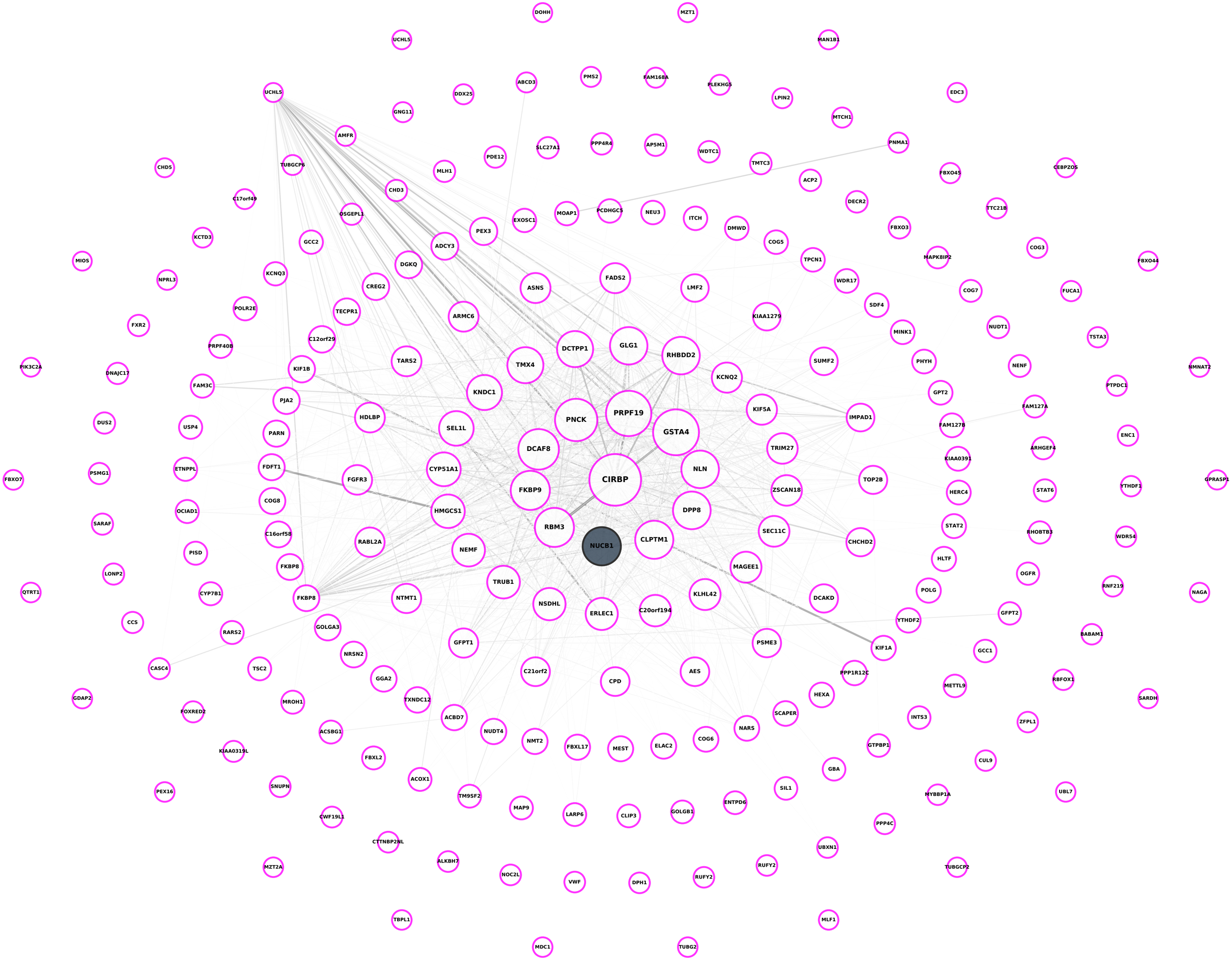
Module 7, n = 234,
FDR Corrected pvalue 0.00044895



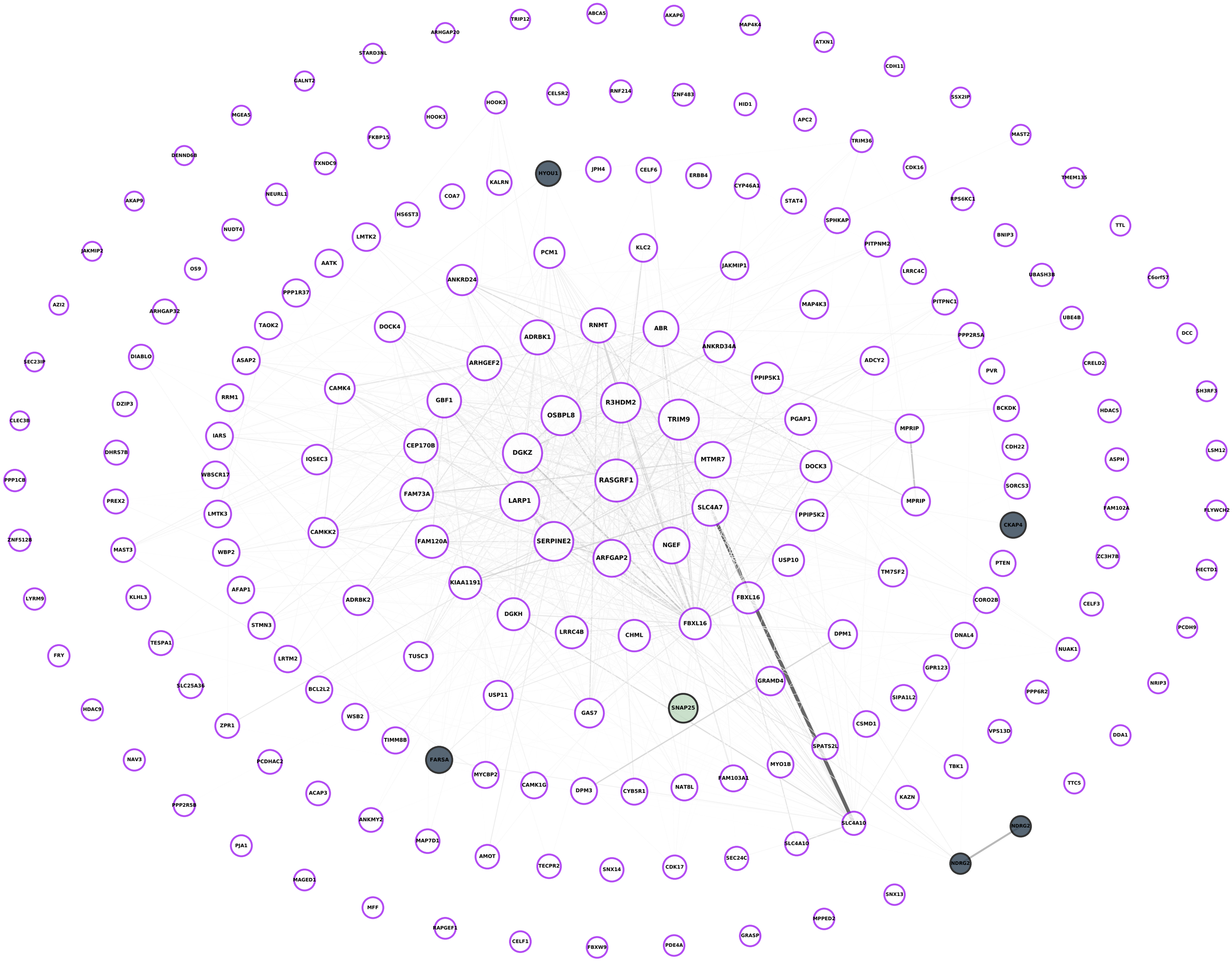
Module 8, n = 232,
FDR Corrected pvalue 0.30558



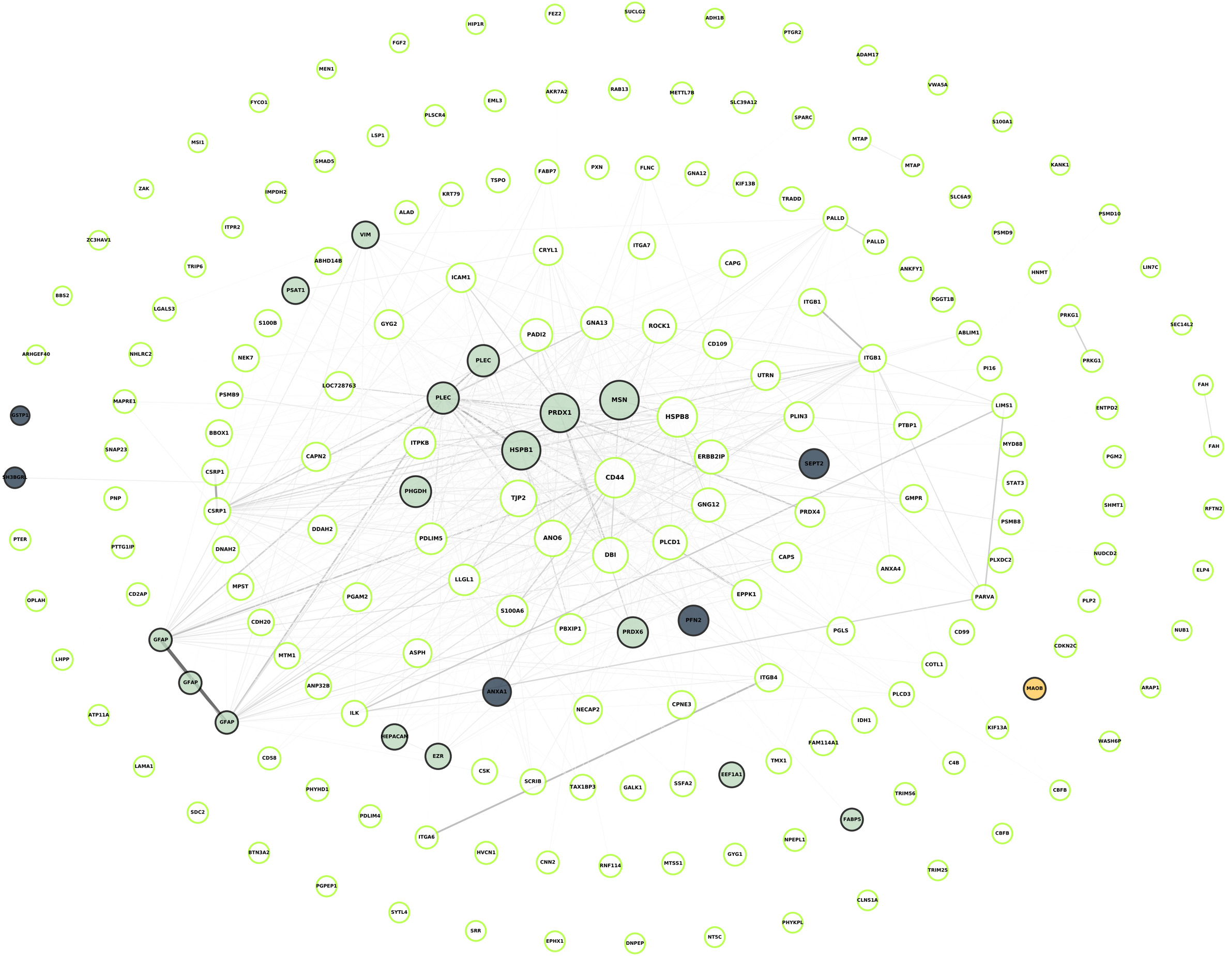
Module 9, n = 227,
FDR Corrected pvalue 1



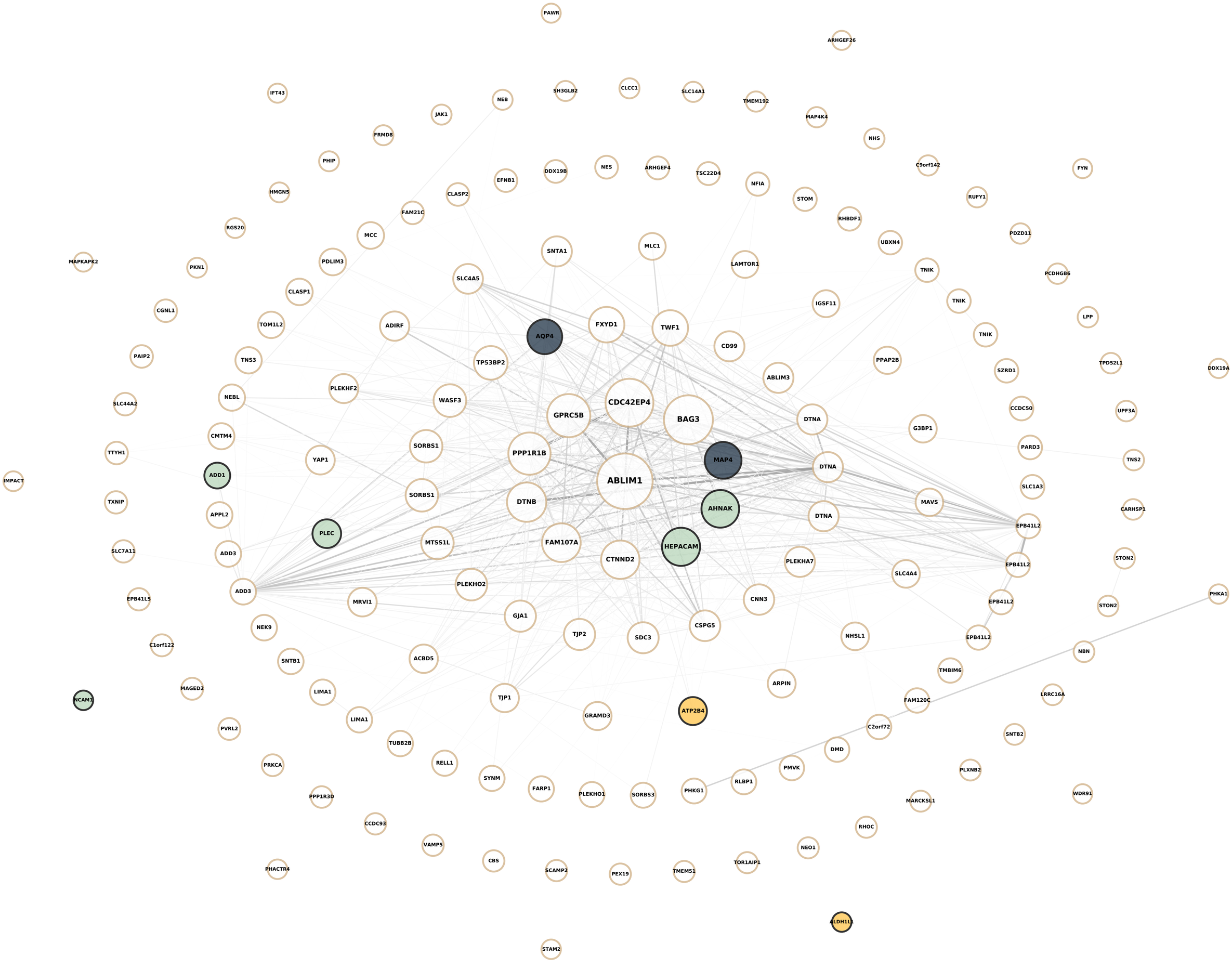
Module 10, n = 200,
FDR Corrected pvalue 1



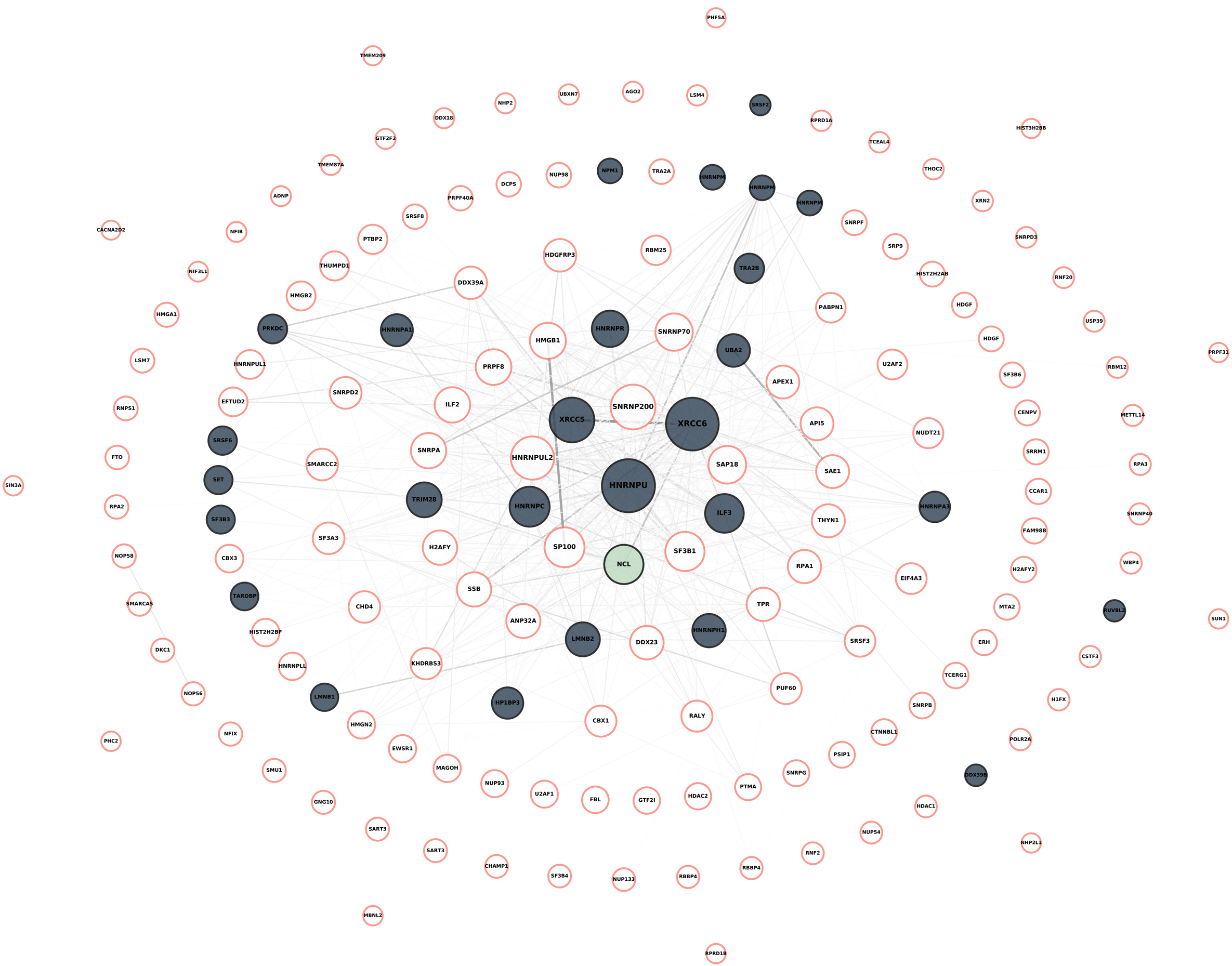
Module 11, n = 198,
FDR Corrected pvalue 0.094128



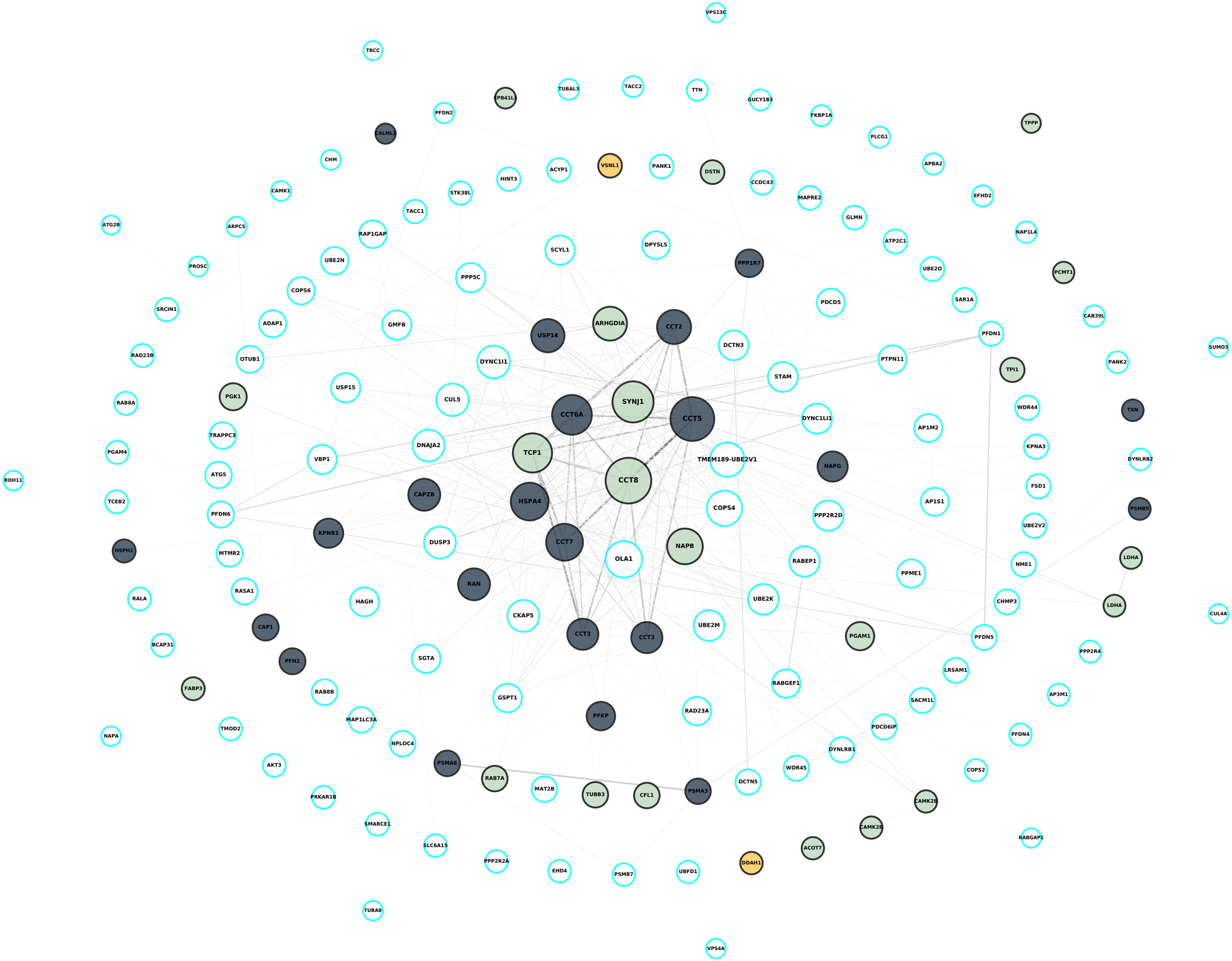
Module 12, n = 164,
FDR Corrected pvalue 1



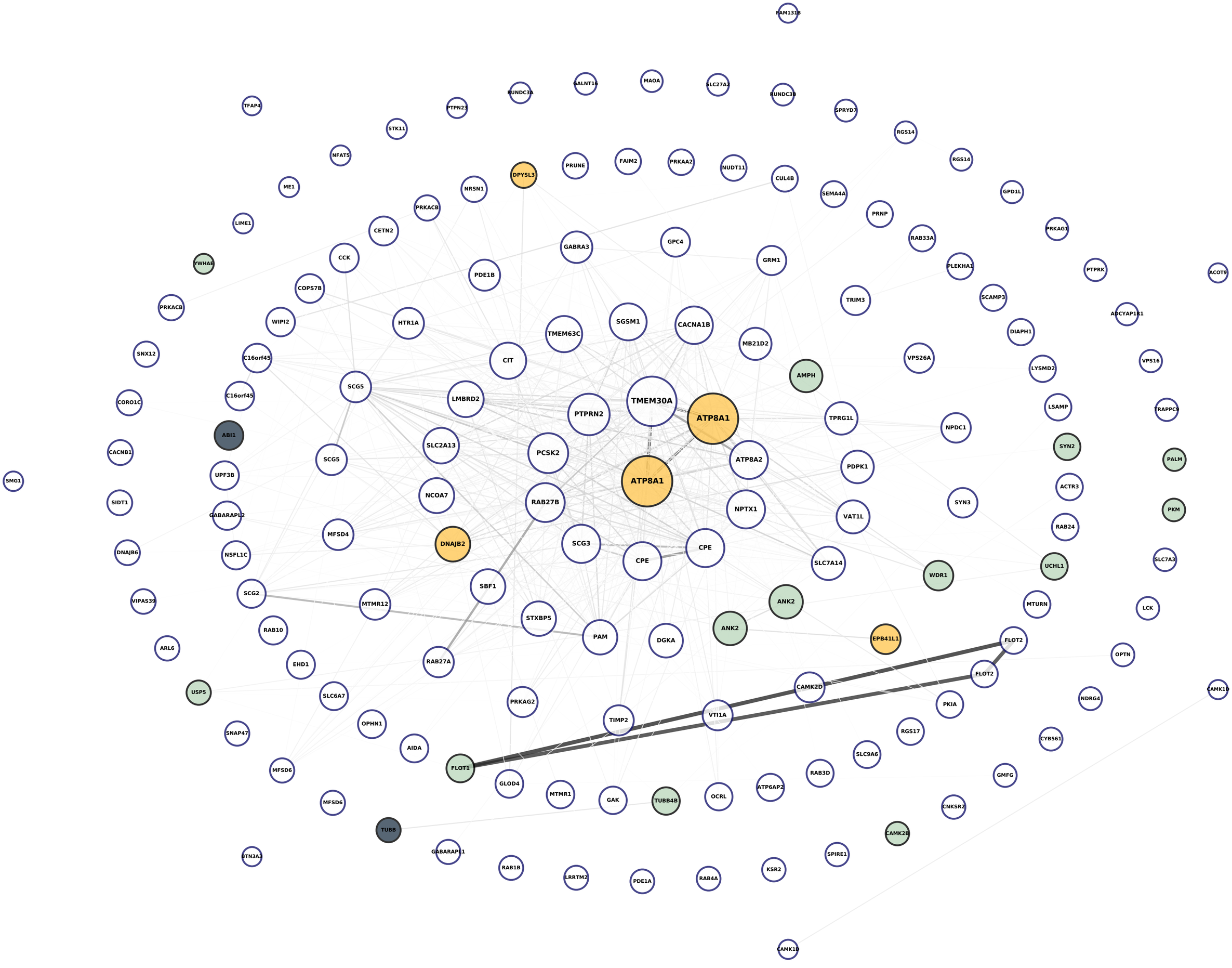
Module 13, n = 162,
FDR Corrected pvalue 1.1211e-05



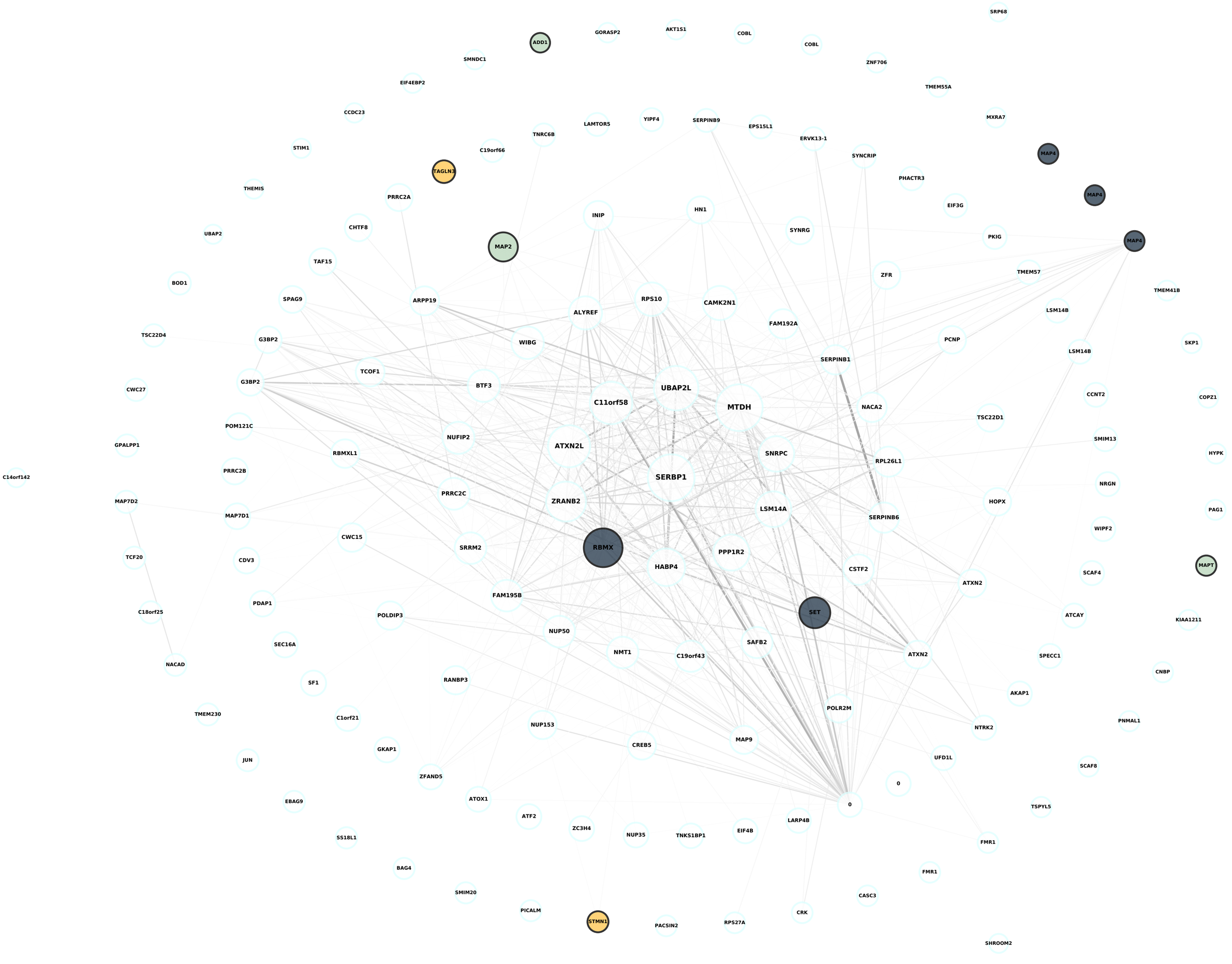
Module 14, n = 162,
FDR Corrected pvalue 4.448e-14



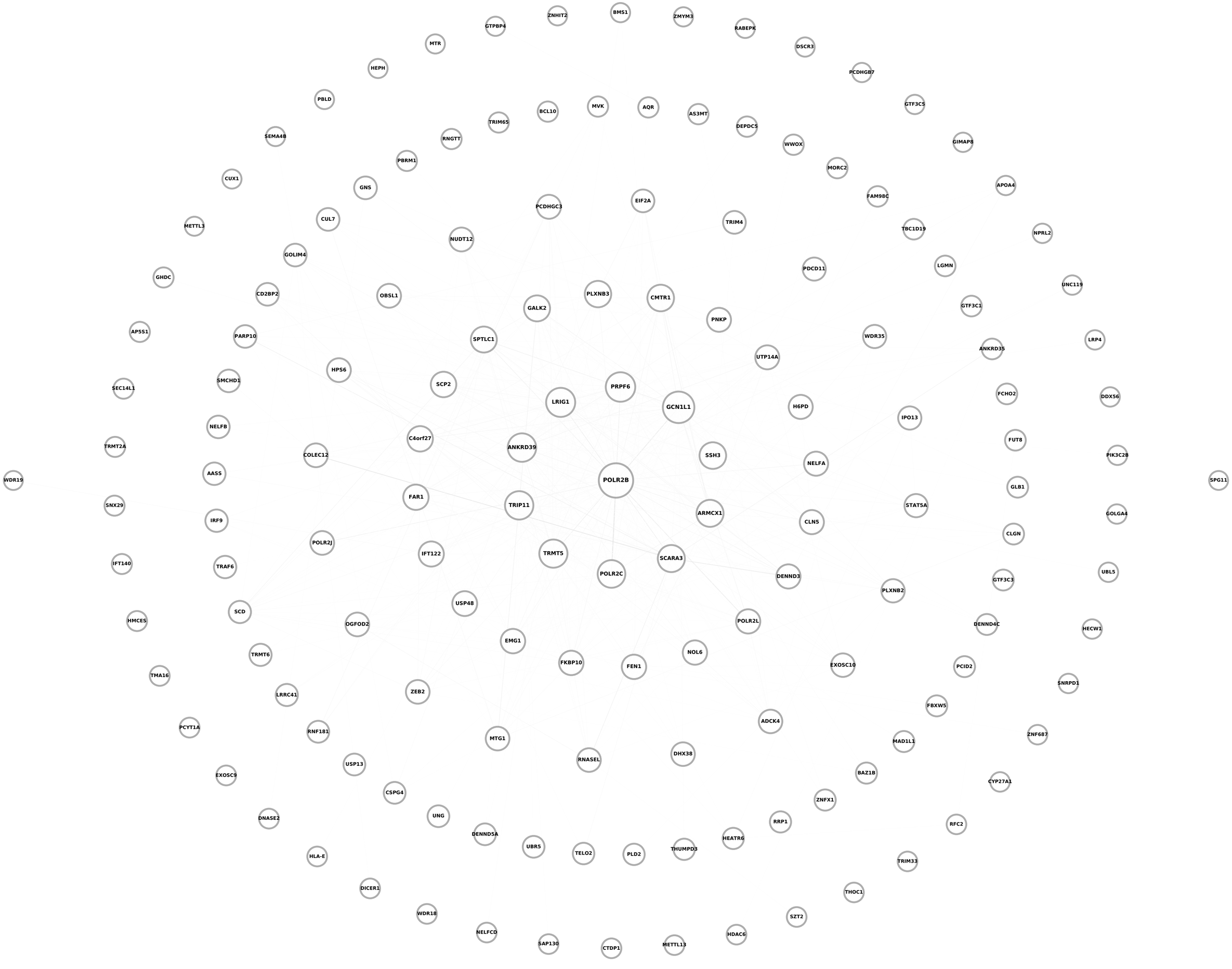
Module 15, n = 158,
FDR Corrected pvalue 0.15687



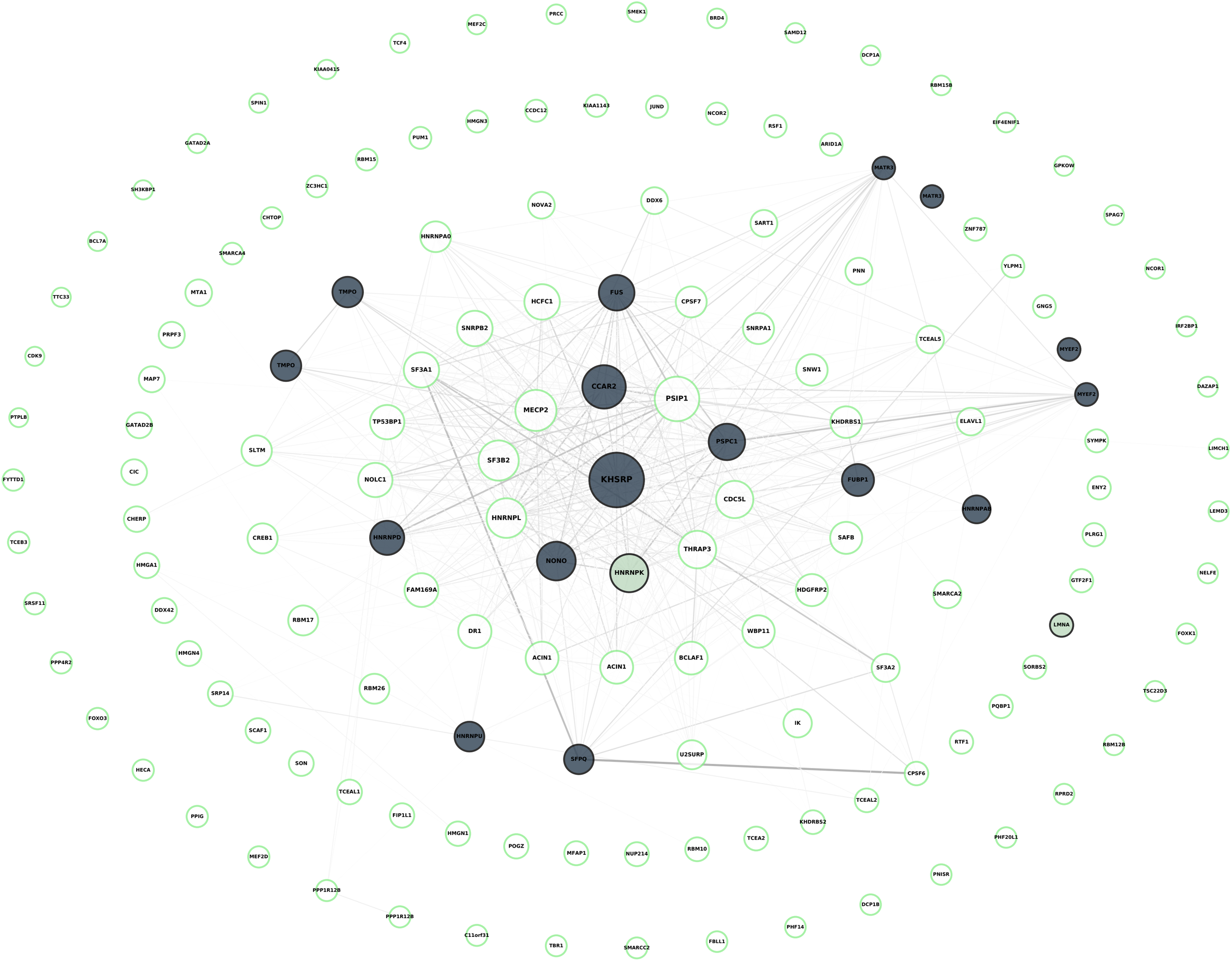
Module 16, n = 154,
FDR Corrected pvalue 1



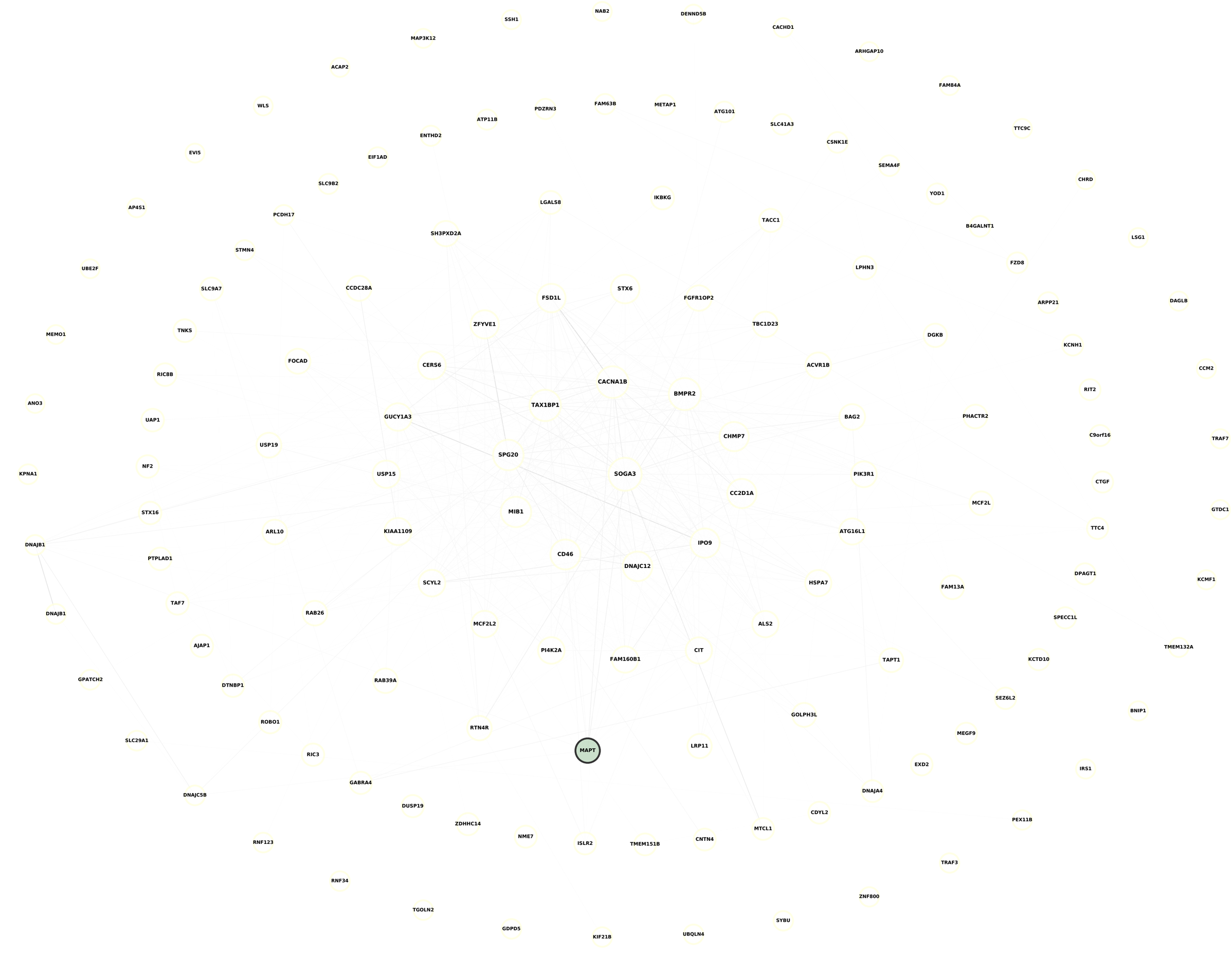
Module 17, n = 153,
FDR Corrected pvalue 1



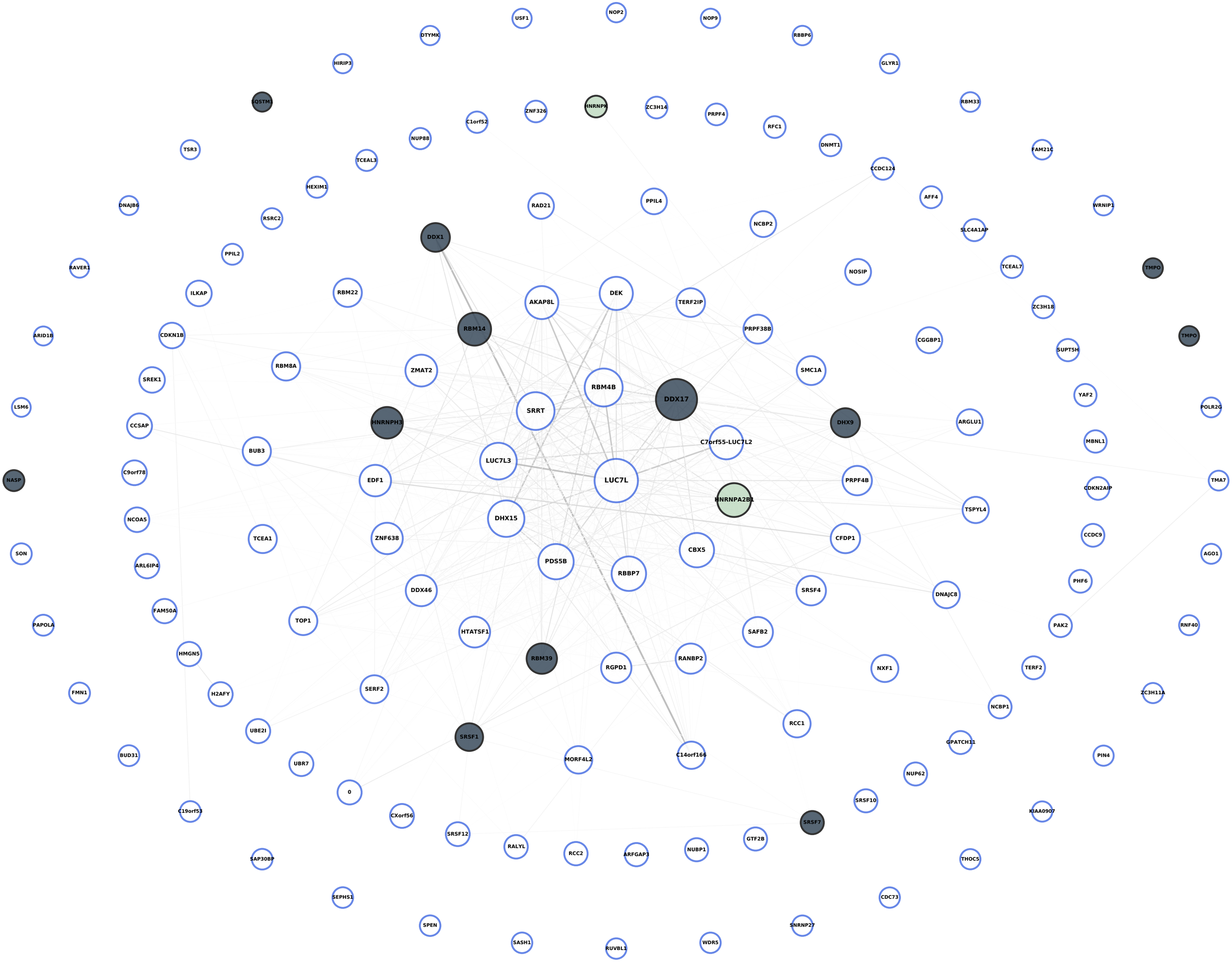
Module 18, n = 148,
FDR Corrected pvalue 0.074783



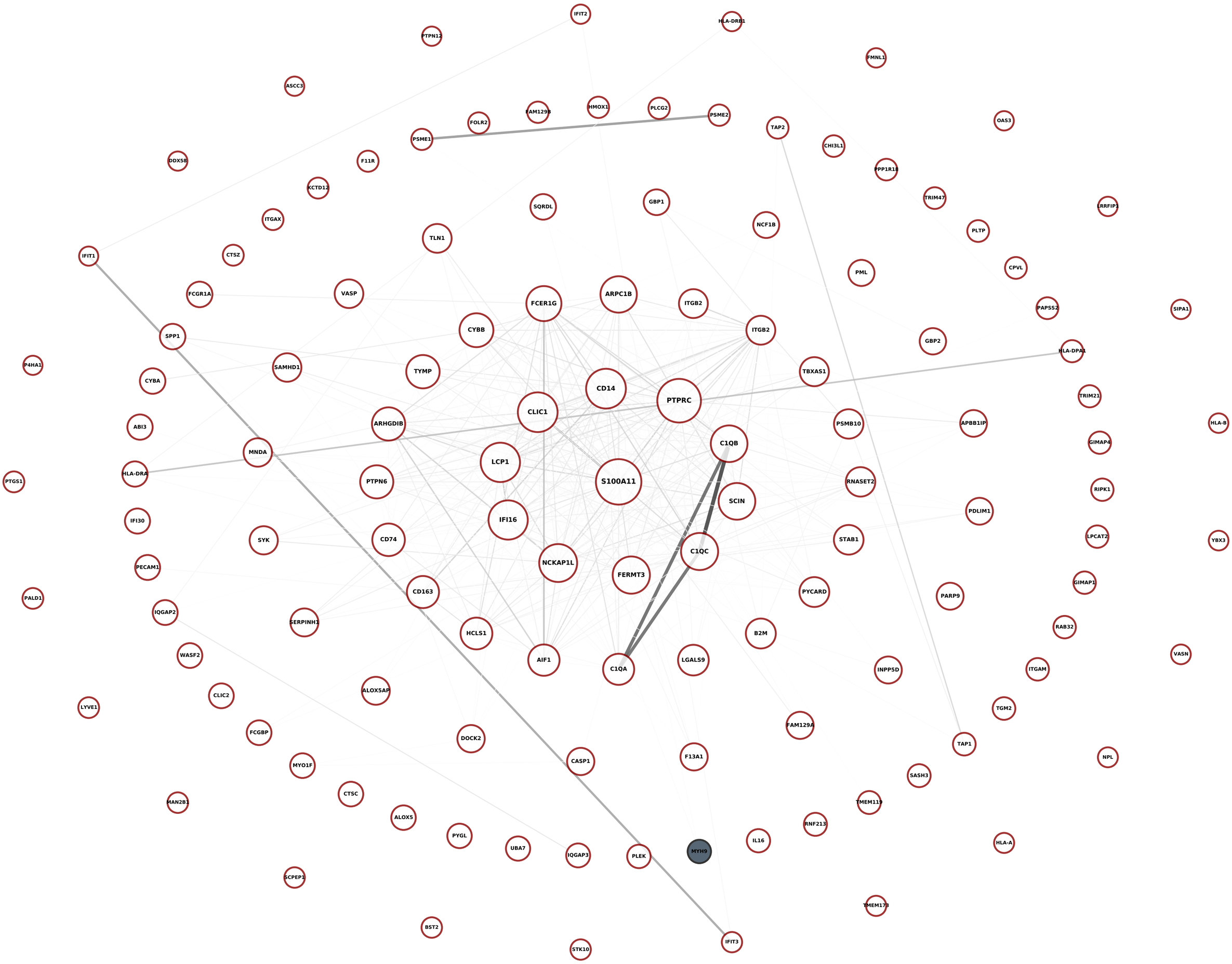
Module 19, n = 142,
FDR Corrected pvalue 1



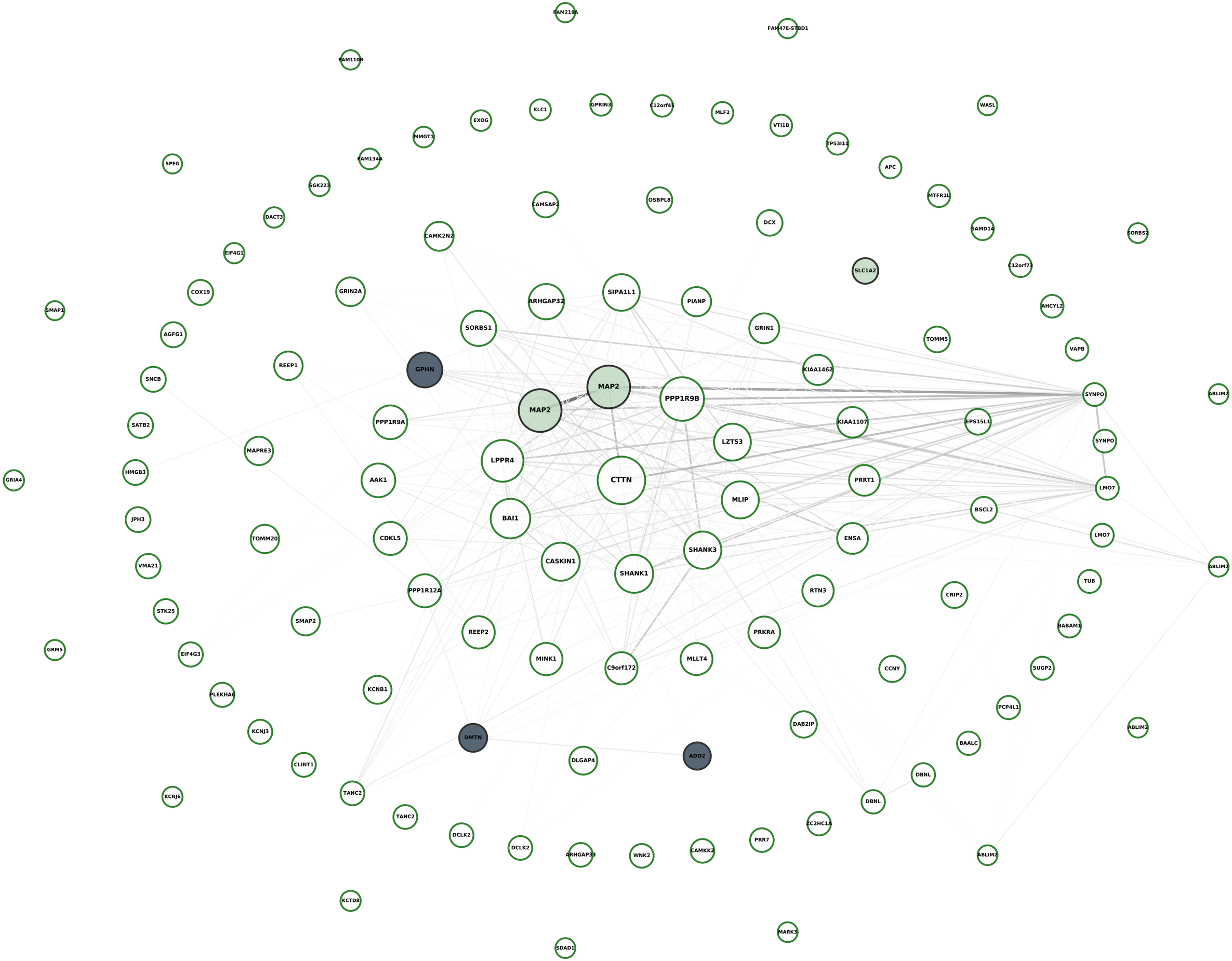
Module 20, n = 141,
FDR Corrected pvalue 0.19461



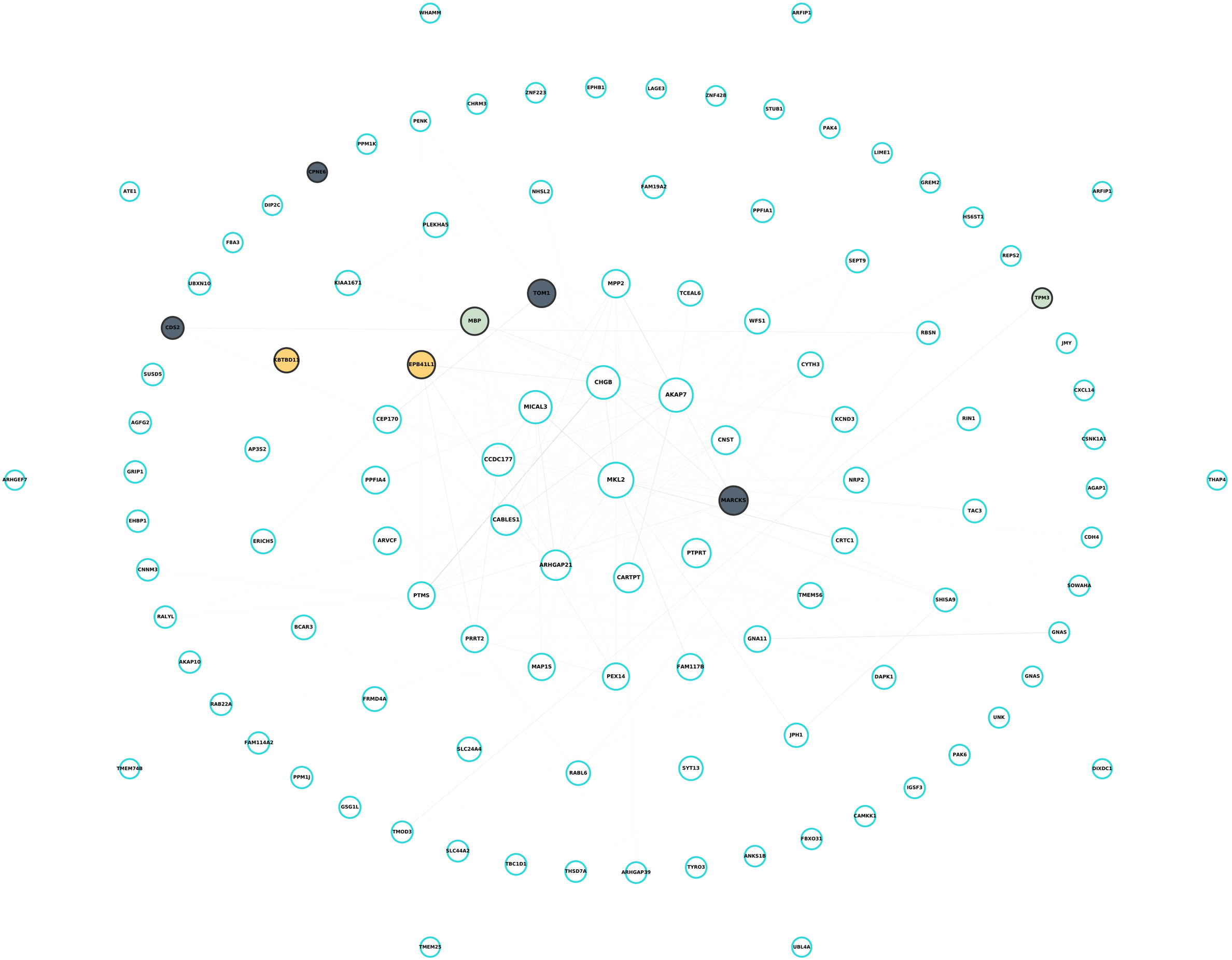
Module 21, n = 126,
FDR Corrected pvalue 1



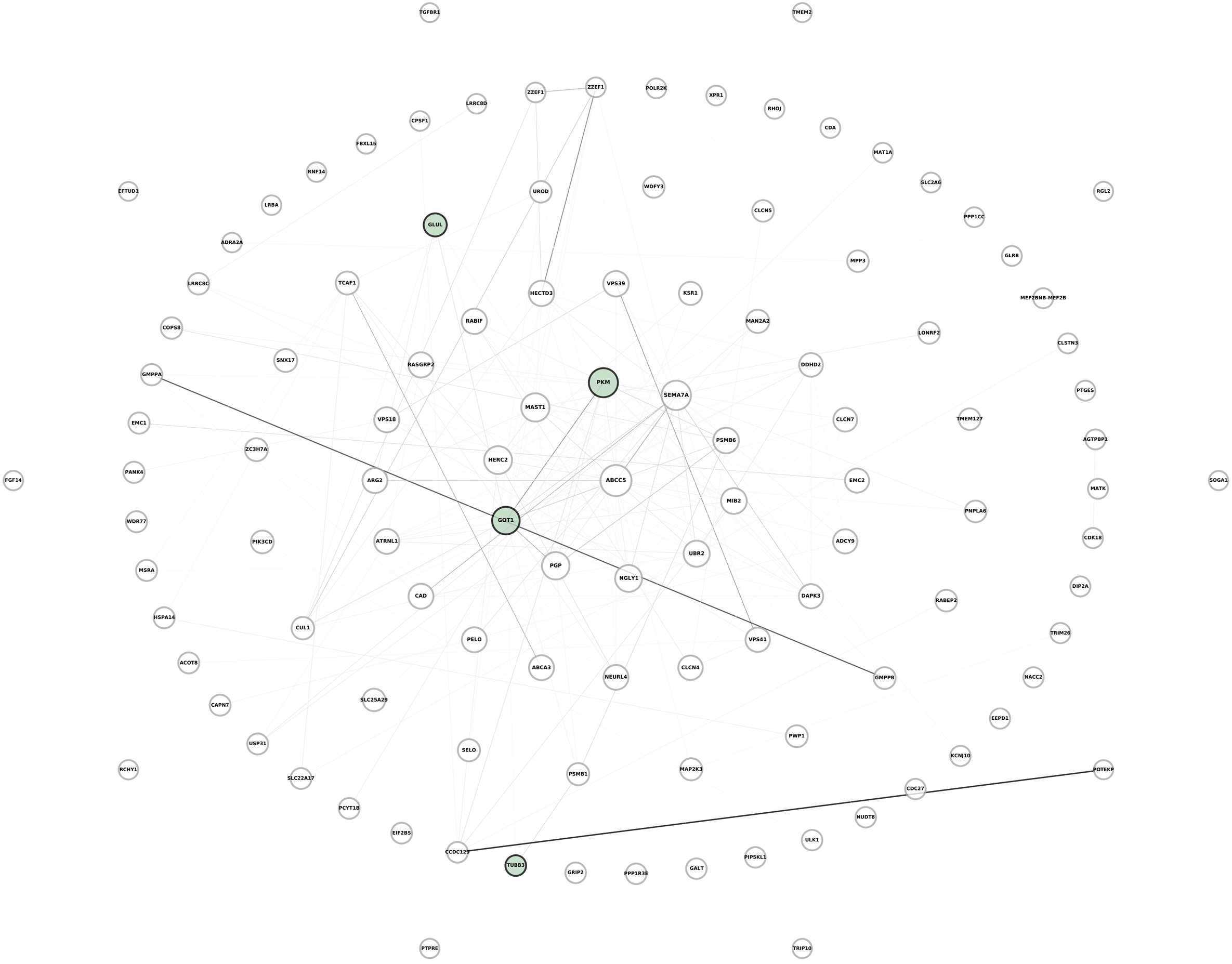
Module 22, n = 118,
FDR Corrected pvalue 1



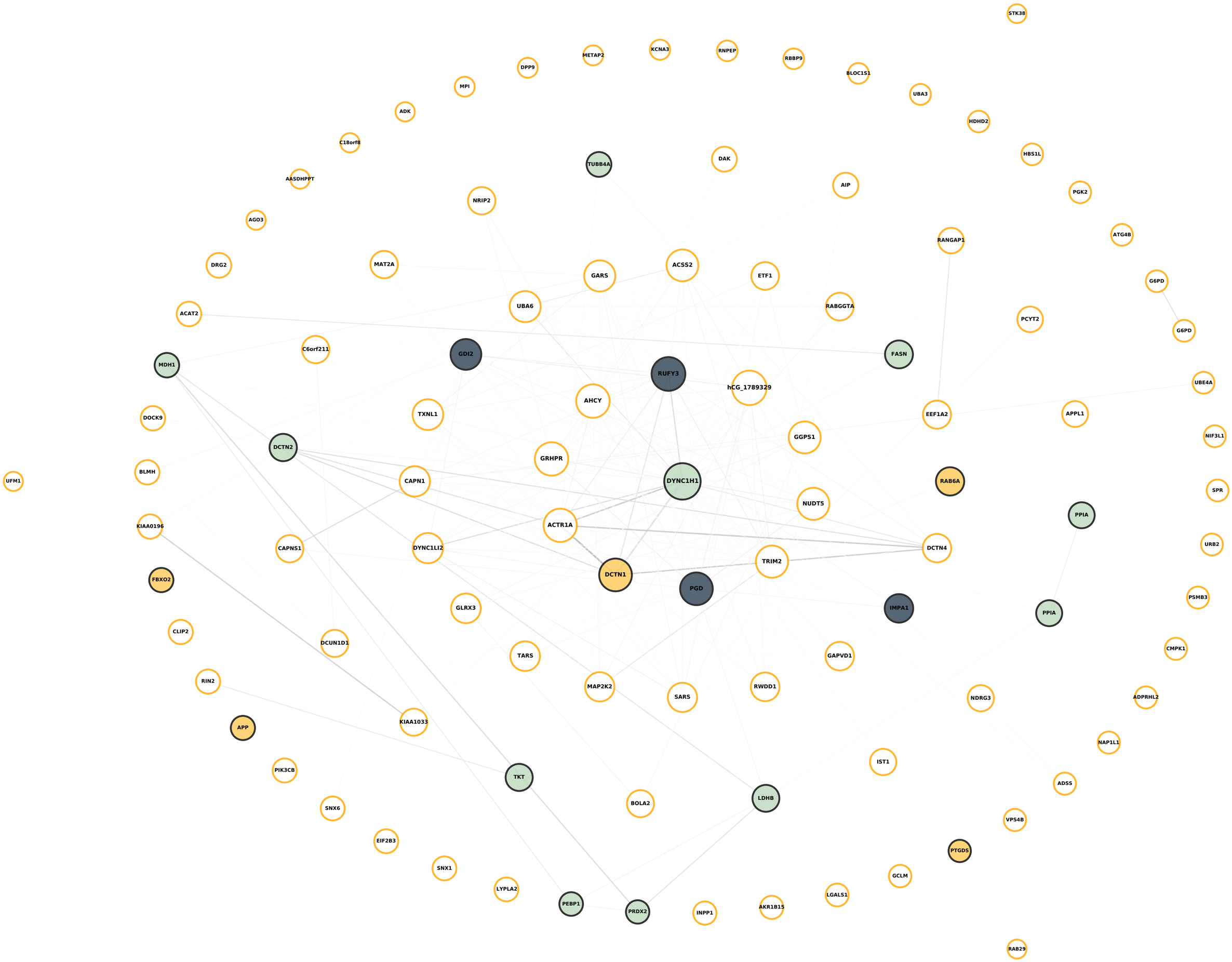
Module 23, n = 111,
FDR Corrected pvalue 1



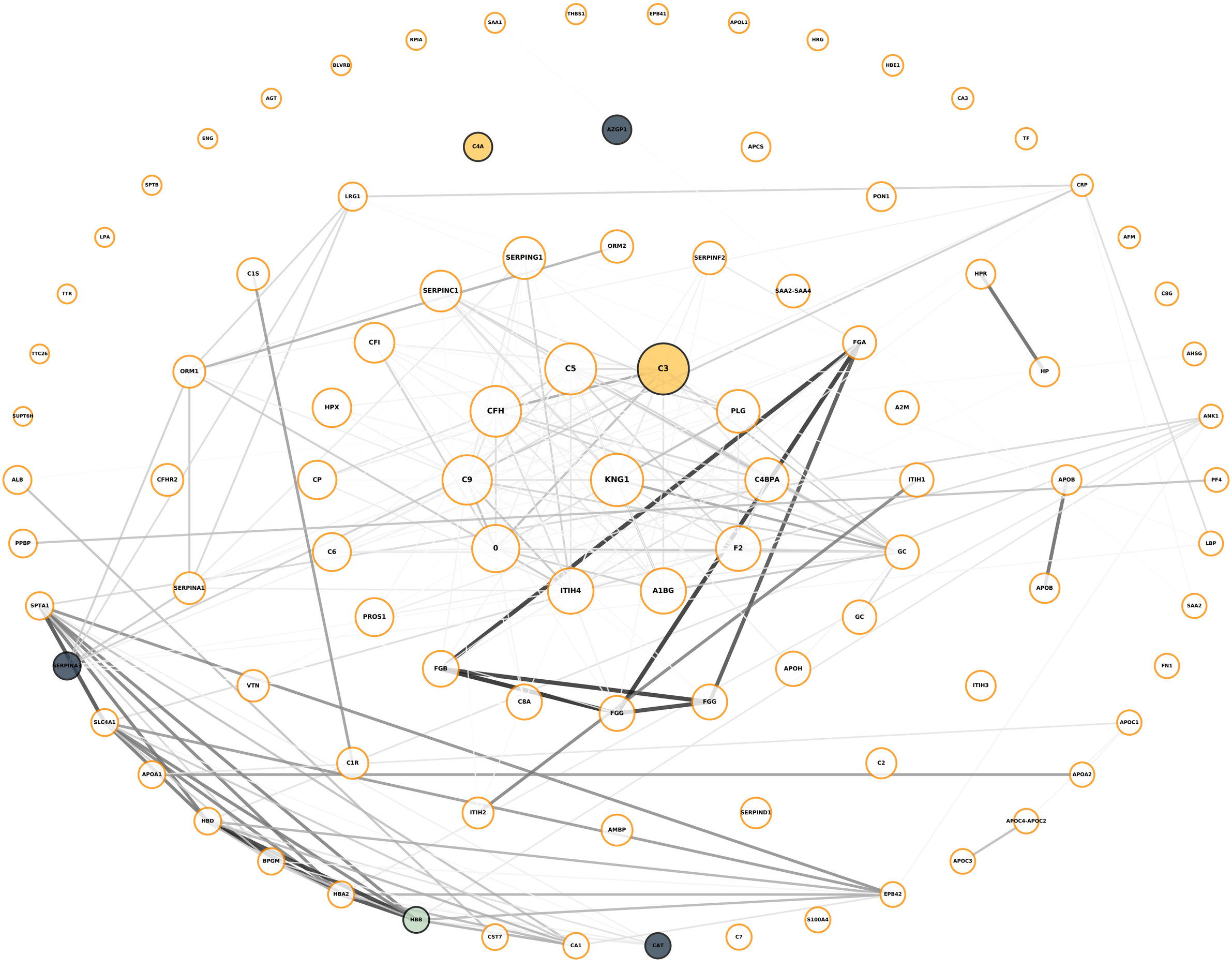
Module 24, n = 111,
FDR Corrected pvalue 1



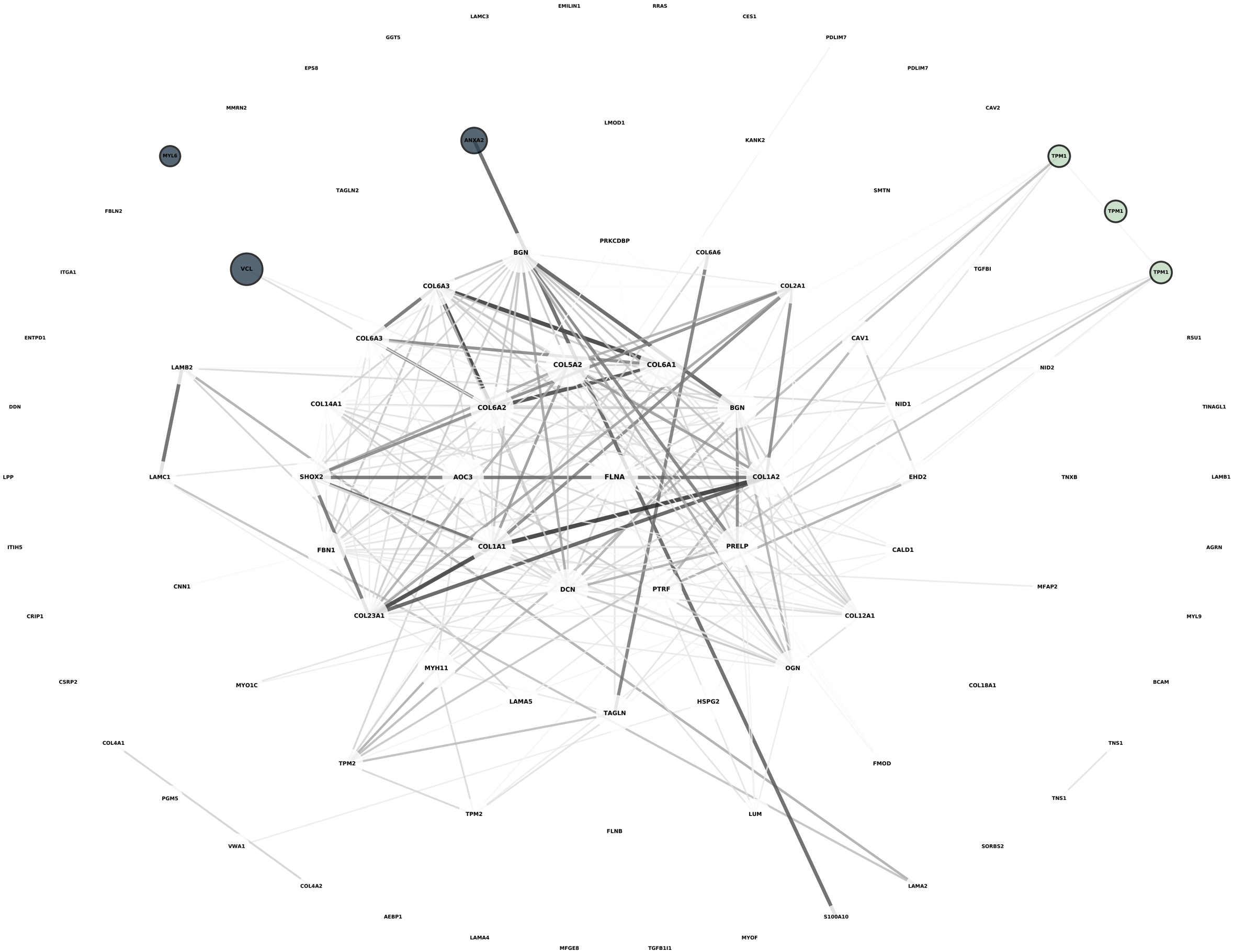
Module 25, n = 104,
FDR Corrected pvalue 0.012325



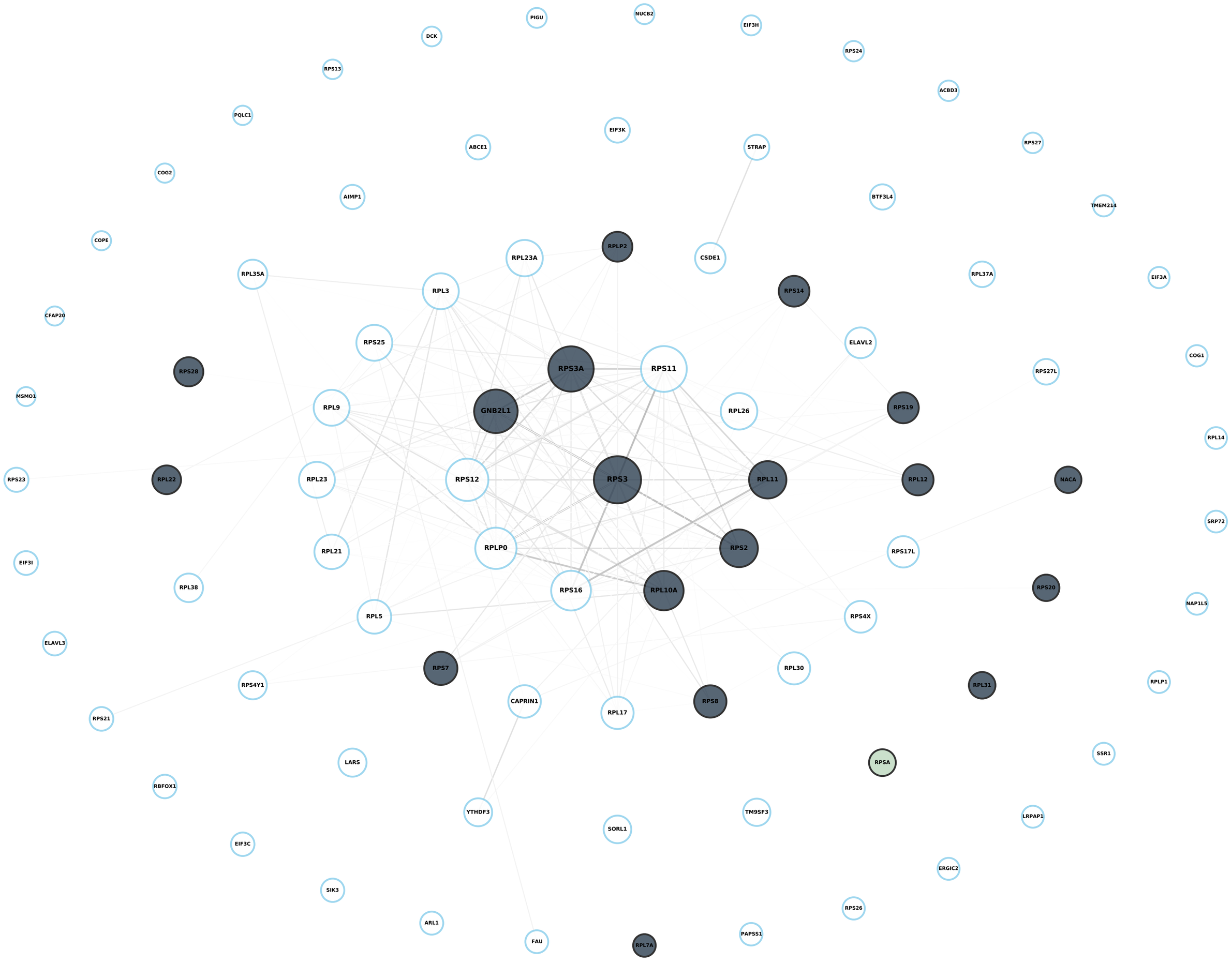
Module 26, n = 97,
FDR Corrected pvalue 1



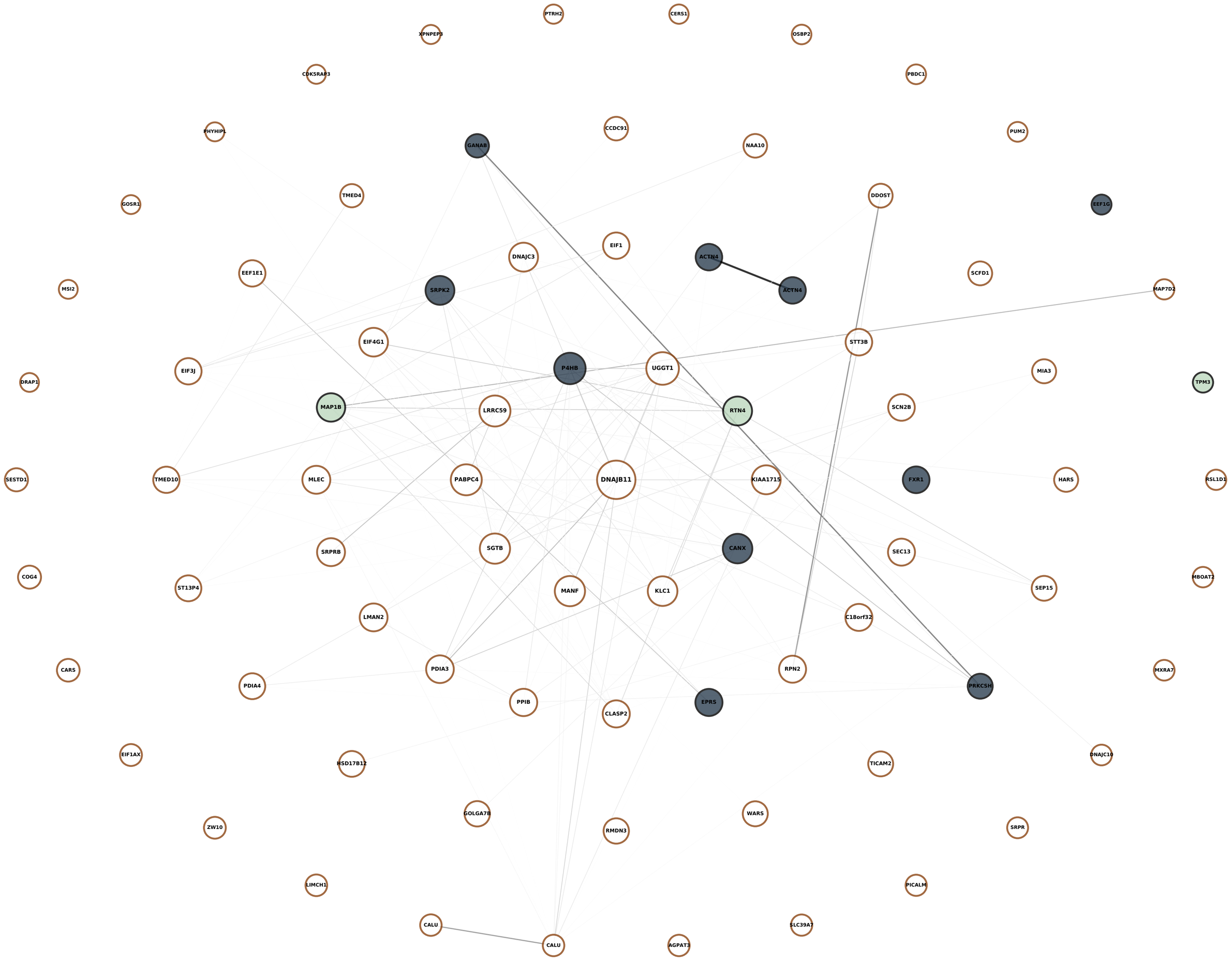
Module 27, n = 93,
FDR Corrected pvalue 1



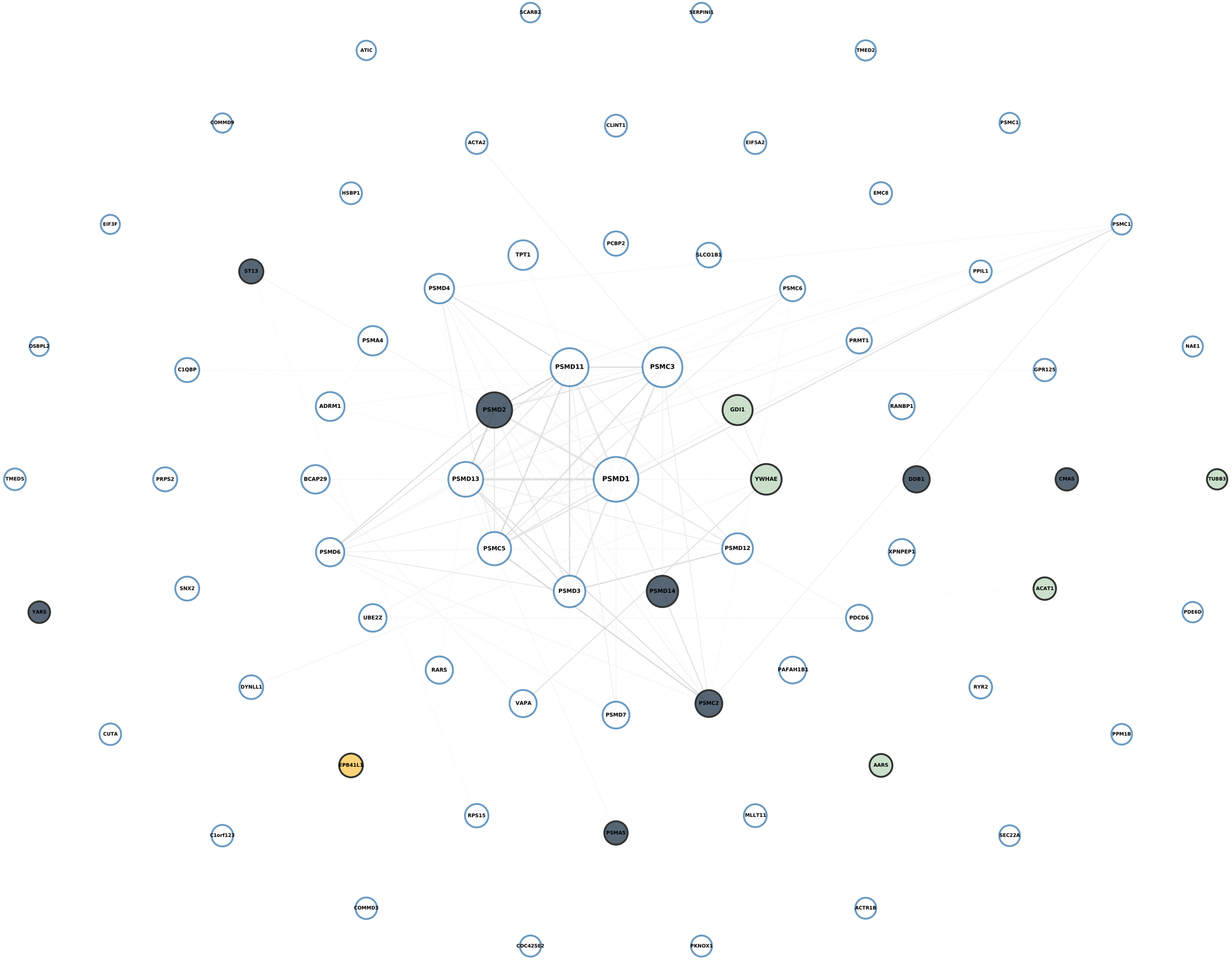
Module 28, n = 86,
FDR Corrected pvalue 3.9464e-06



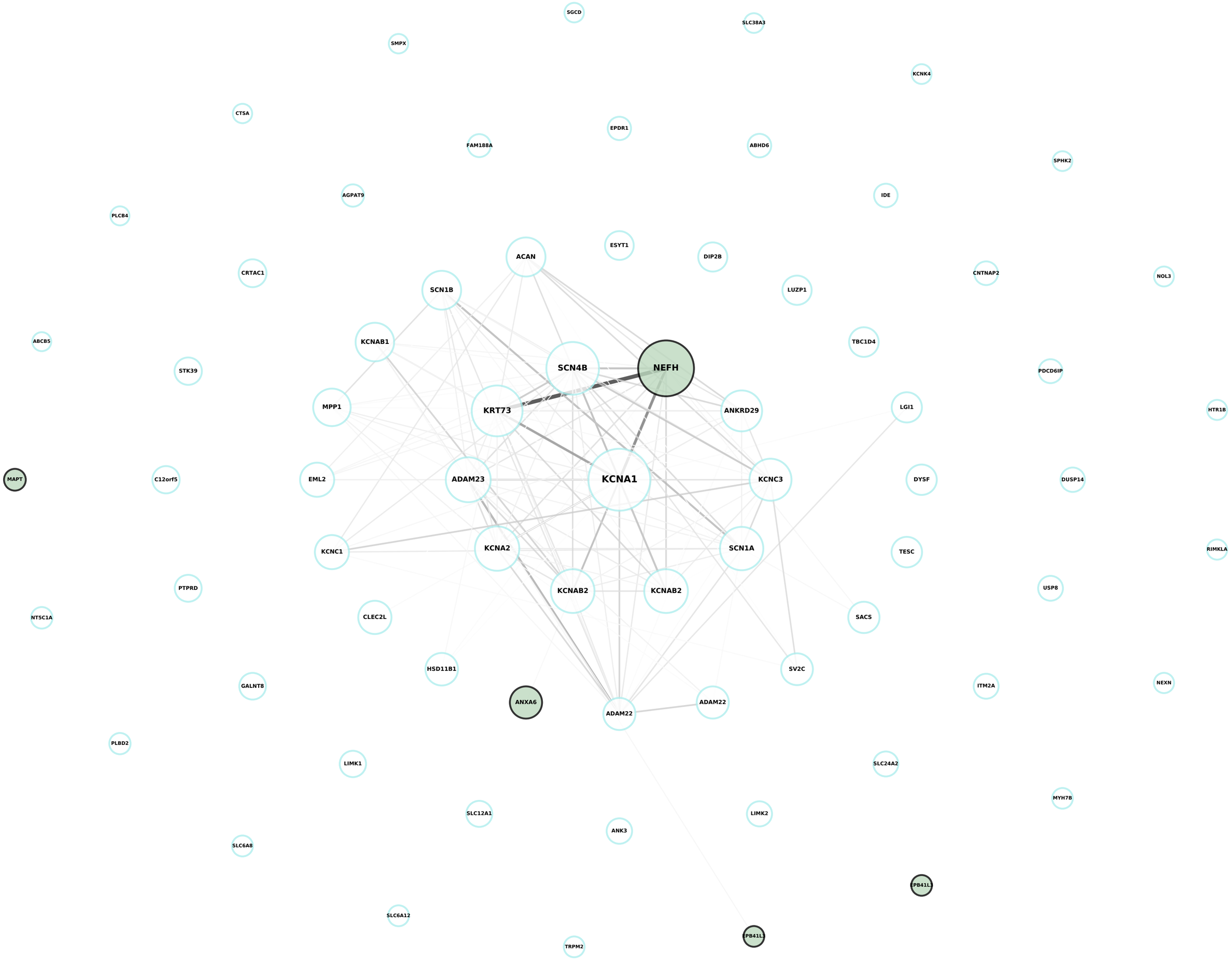
Module 29, n = 81,
FDR Corrected pvalue 0.010991



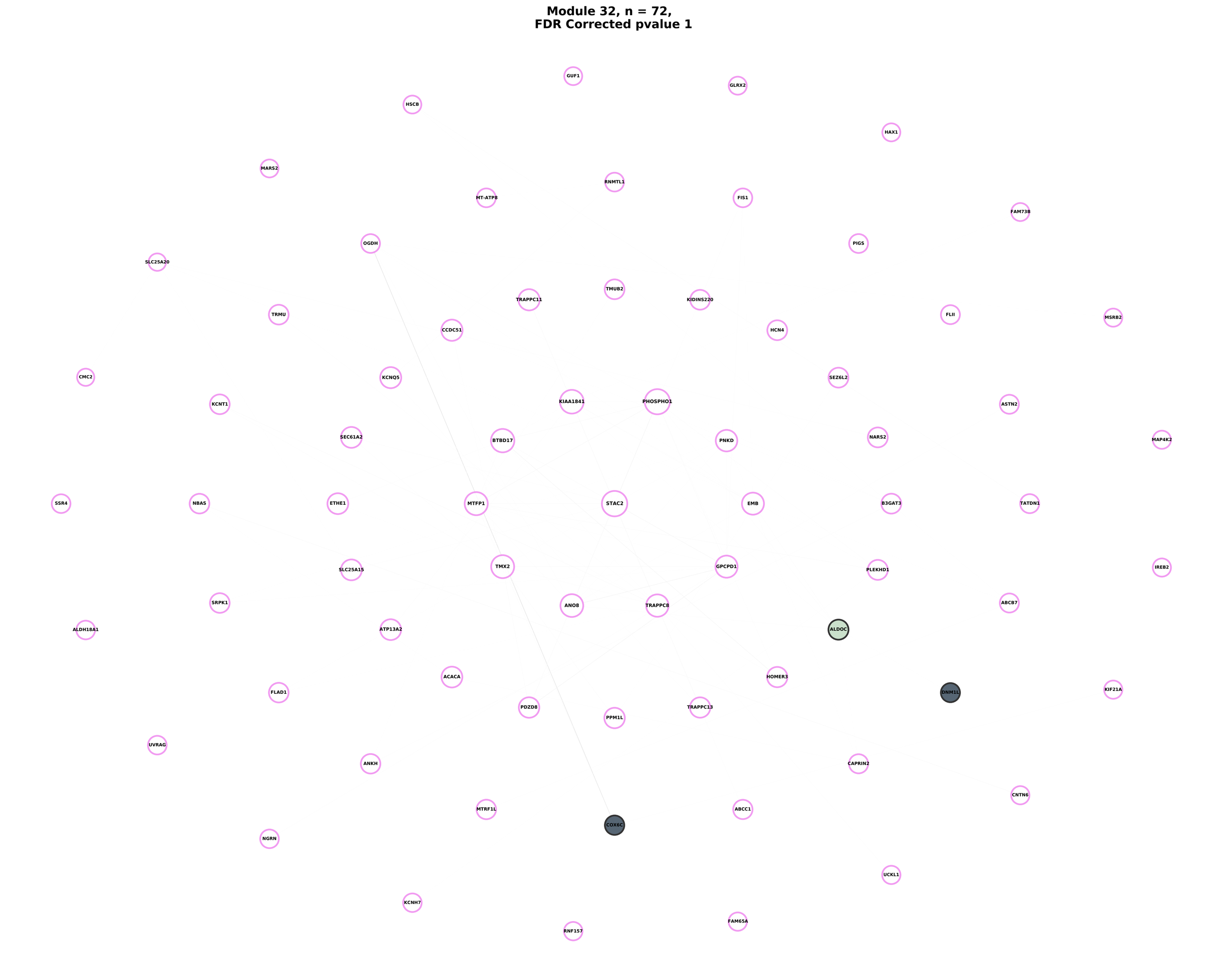
Module 30, n = 73,
FDR Corrected pvalue 0.0016322



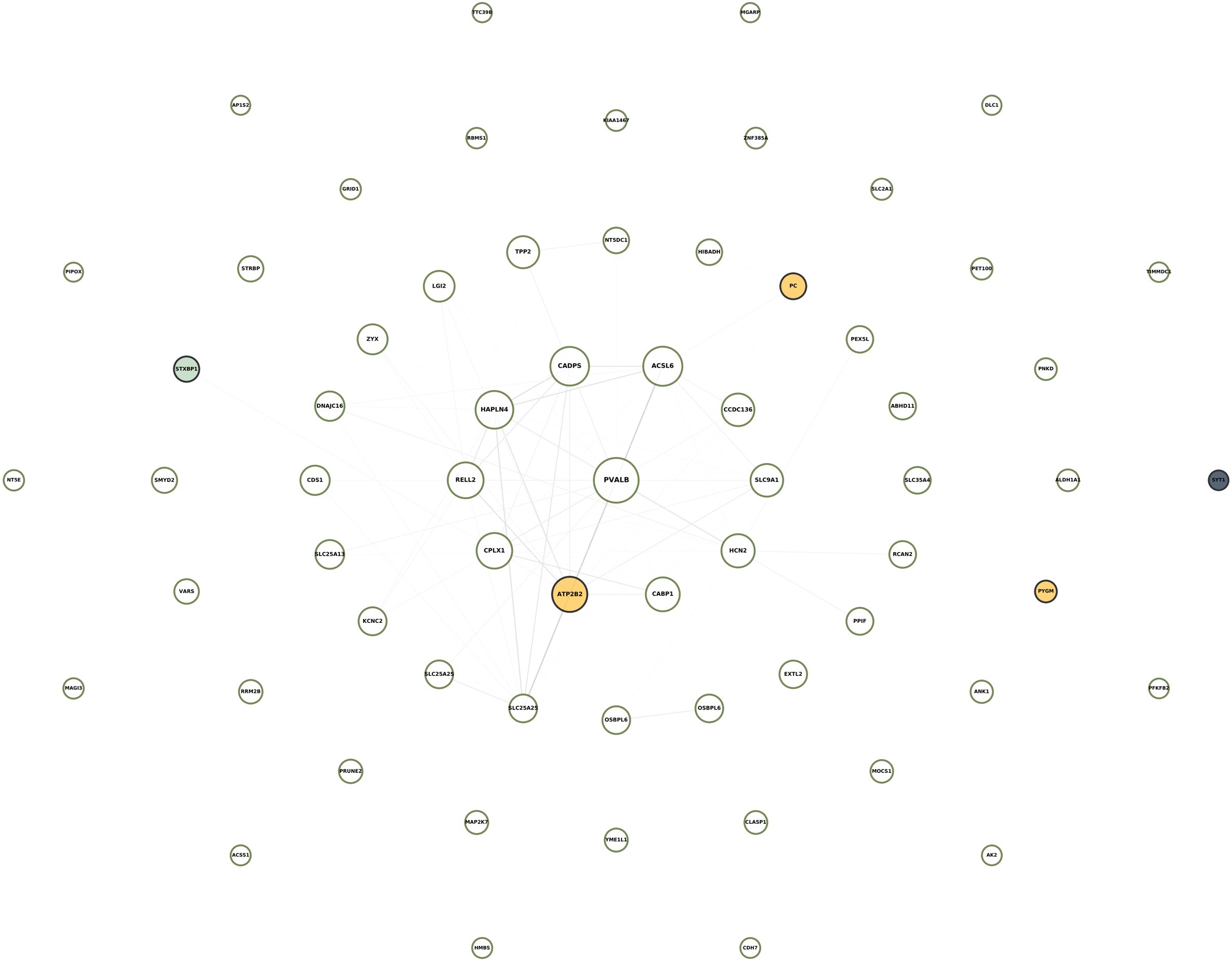
Module 31, n = 72,
FDR Corrected pvalue 0.99401



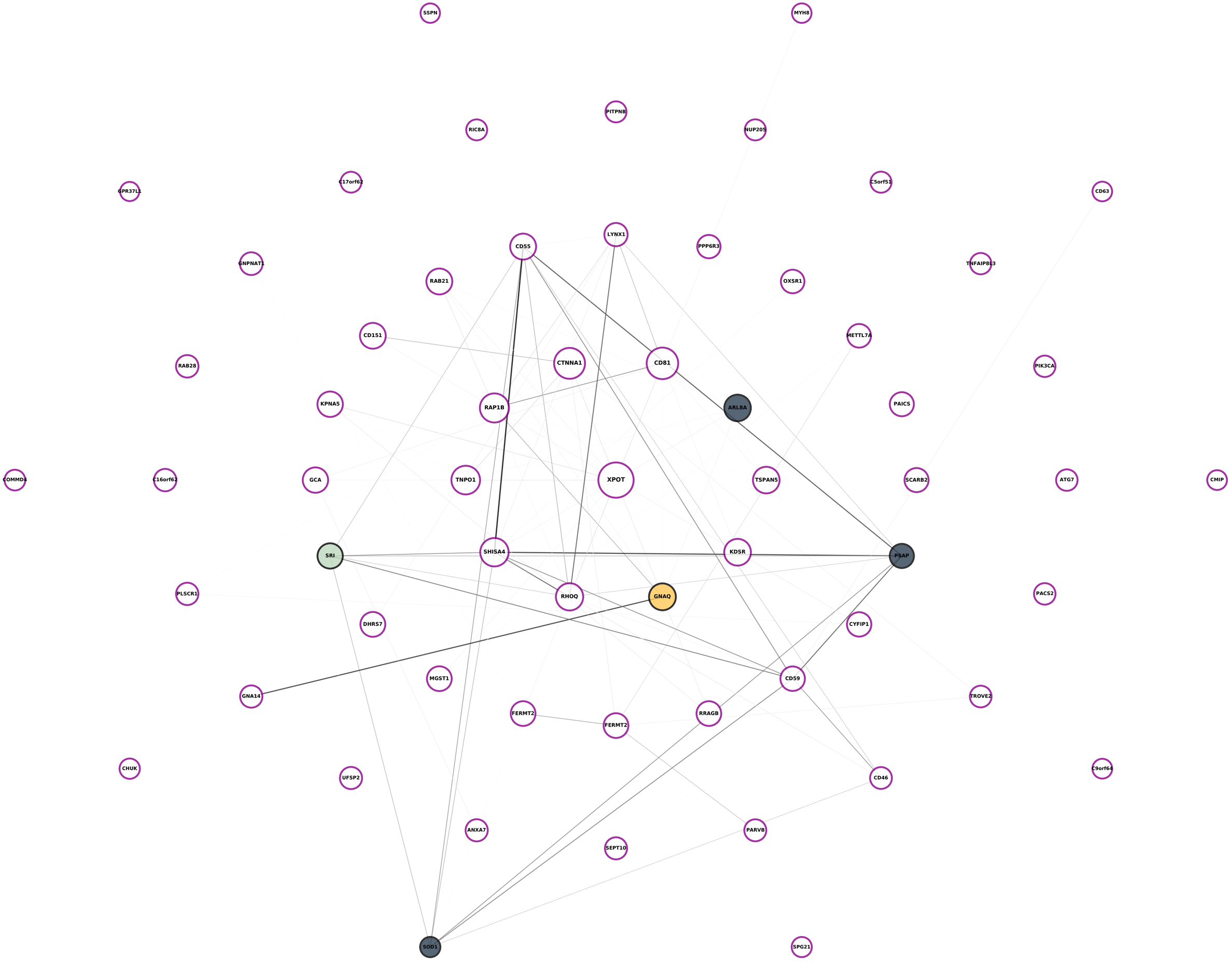
Module 32, n = 72,
FDR Corrected pvalue 1



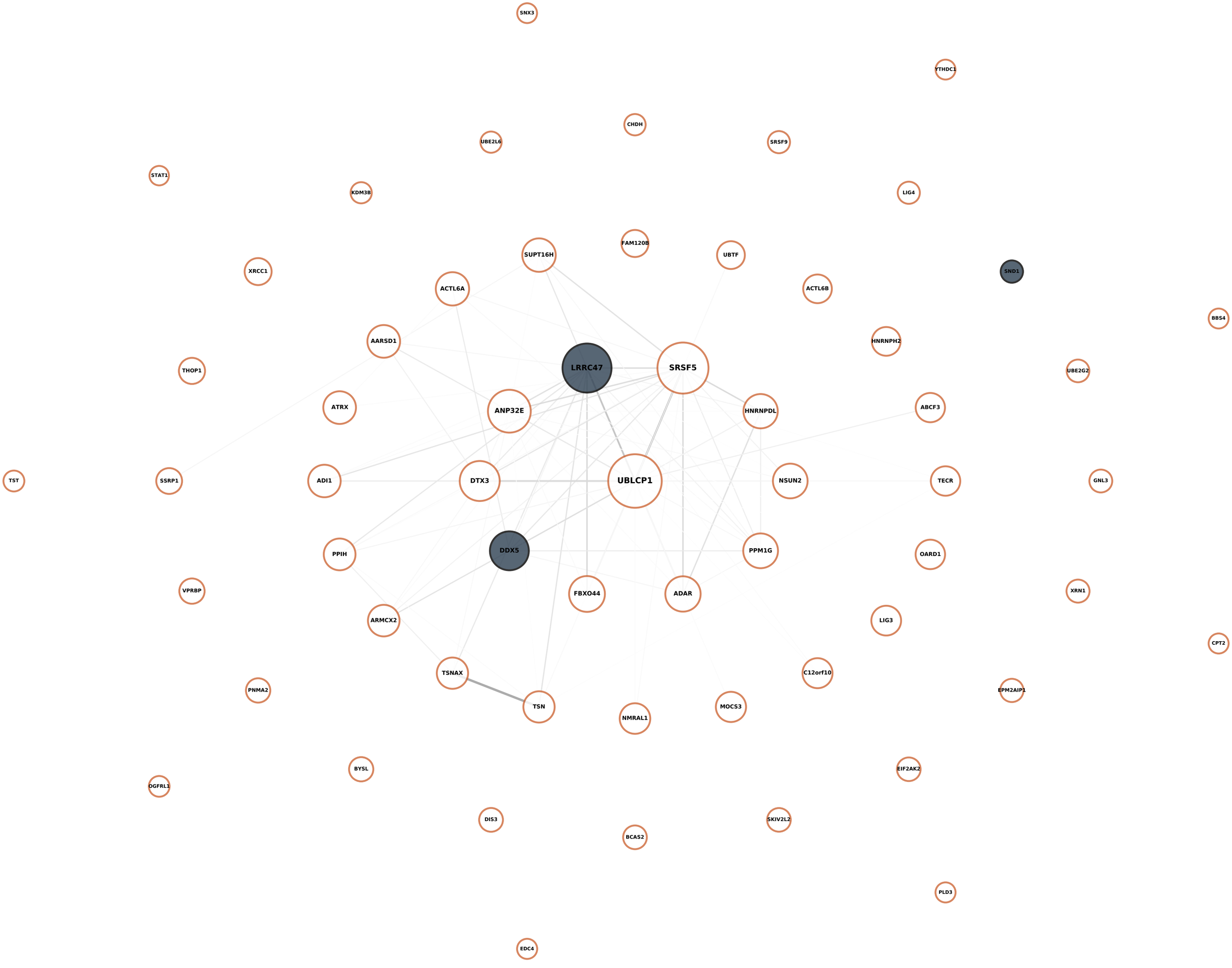
Module 33, n = 65,
FDR Corrected pvalue 1



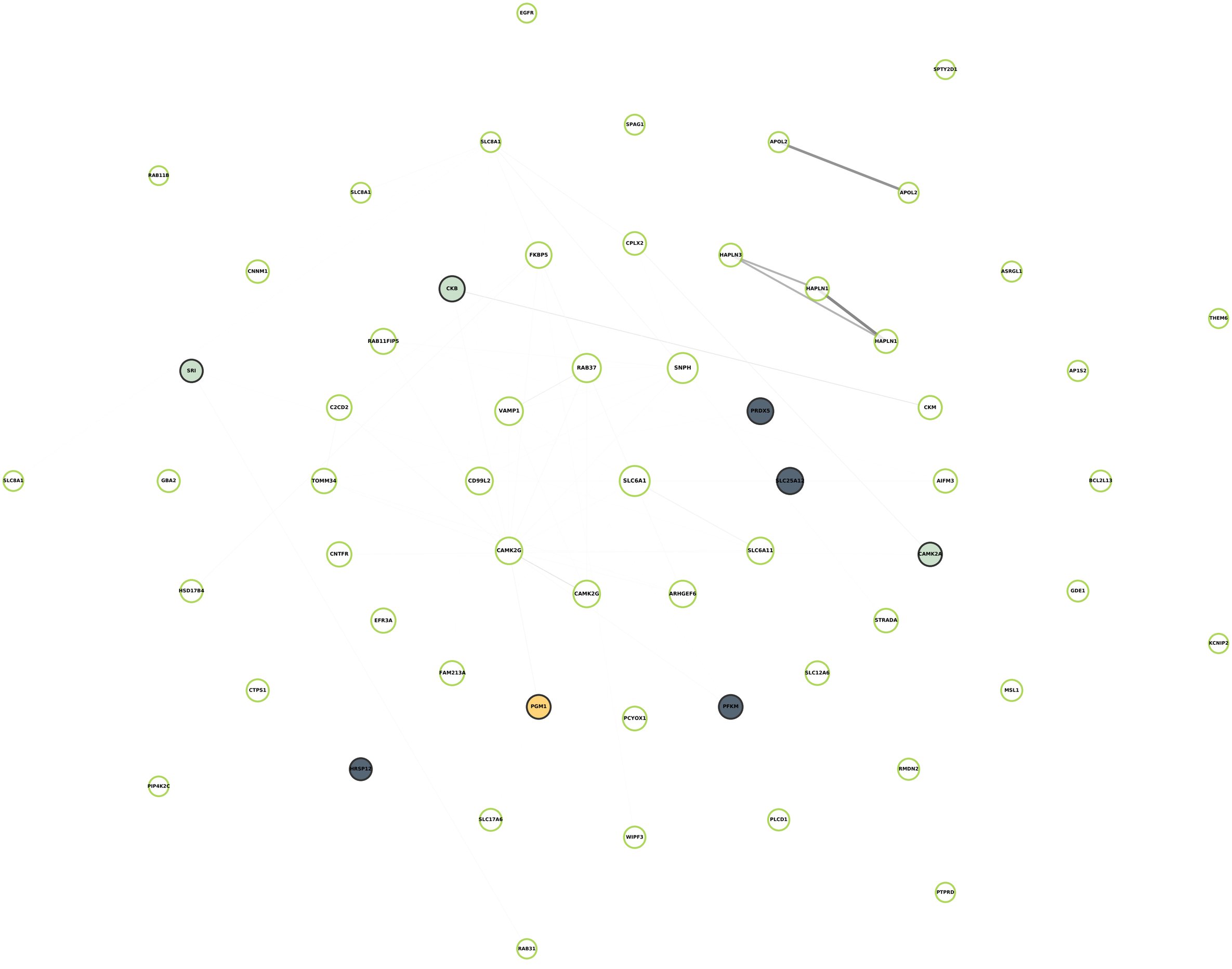
Module 34, n = 61,
FDR Corrected pvalue 0.86525



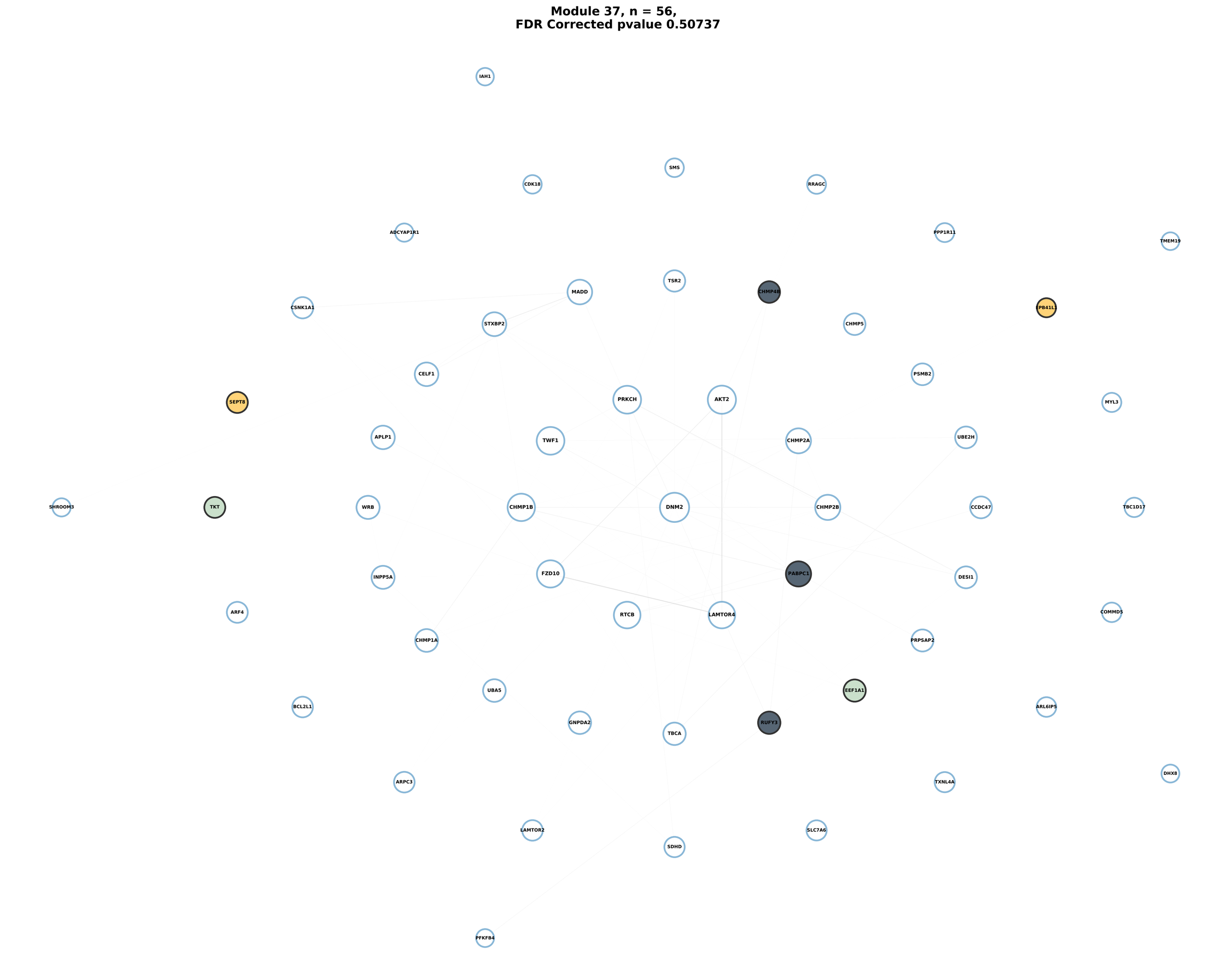
Module 35, n = 60,
FDR Corrected pvalue 1



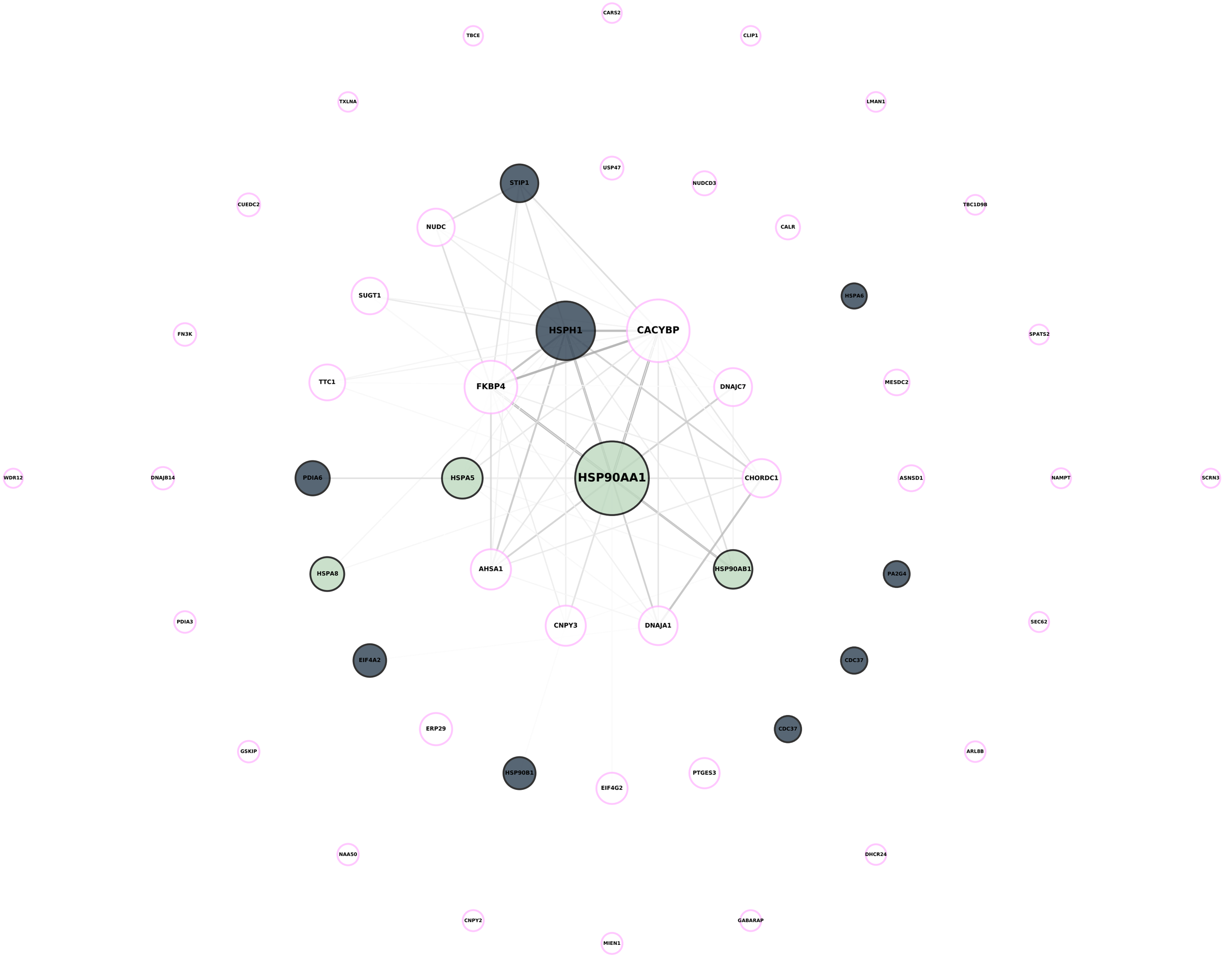
Module 36, n = 60,
FDR Corrected pvalue 0.12774



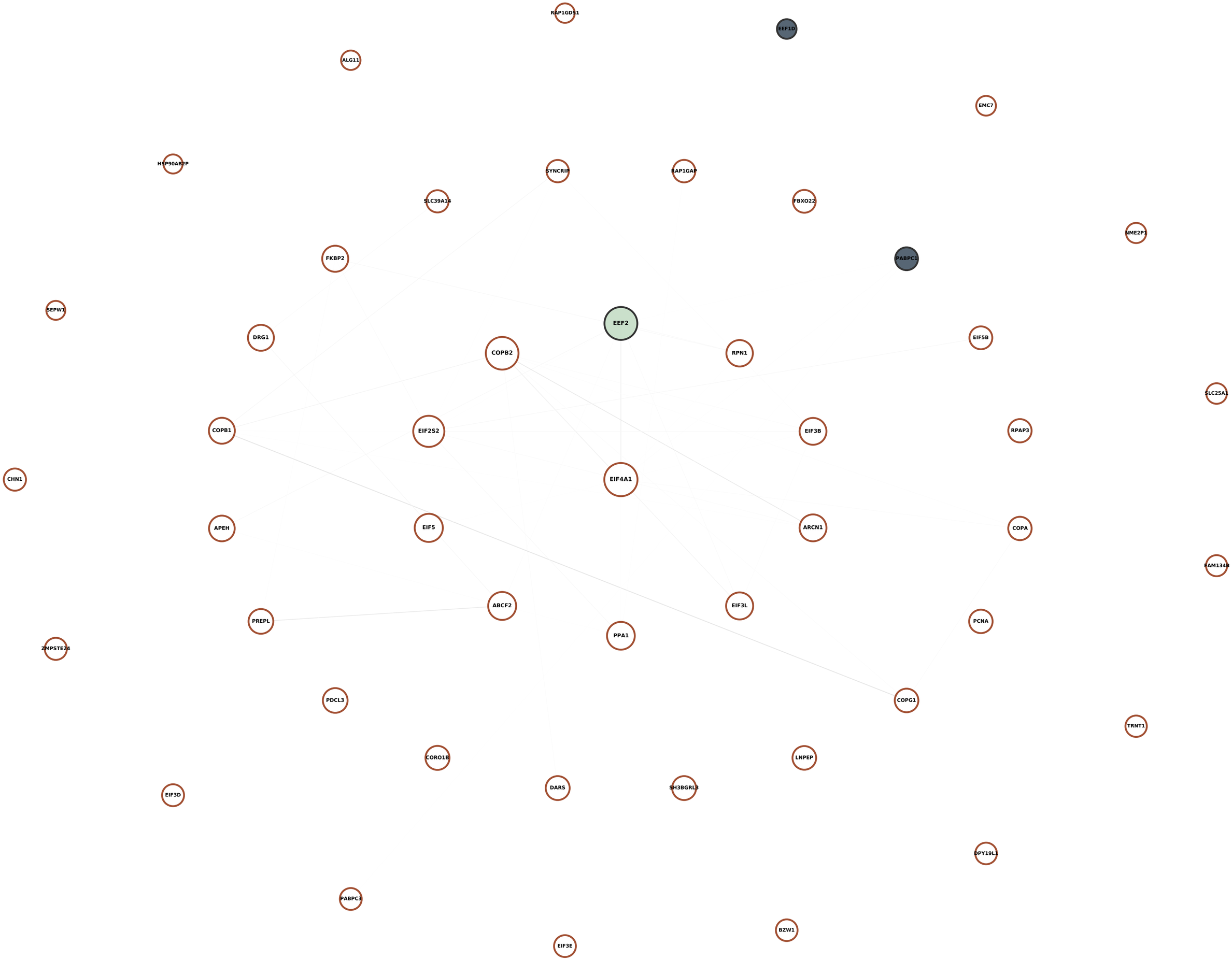
Module 37, n = 56,
FDR Corrected pvalue 0.50737



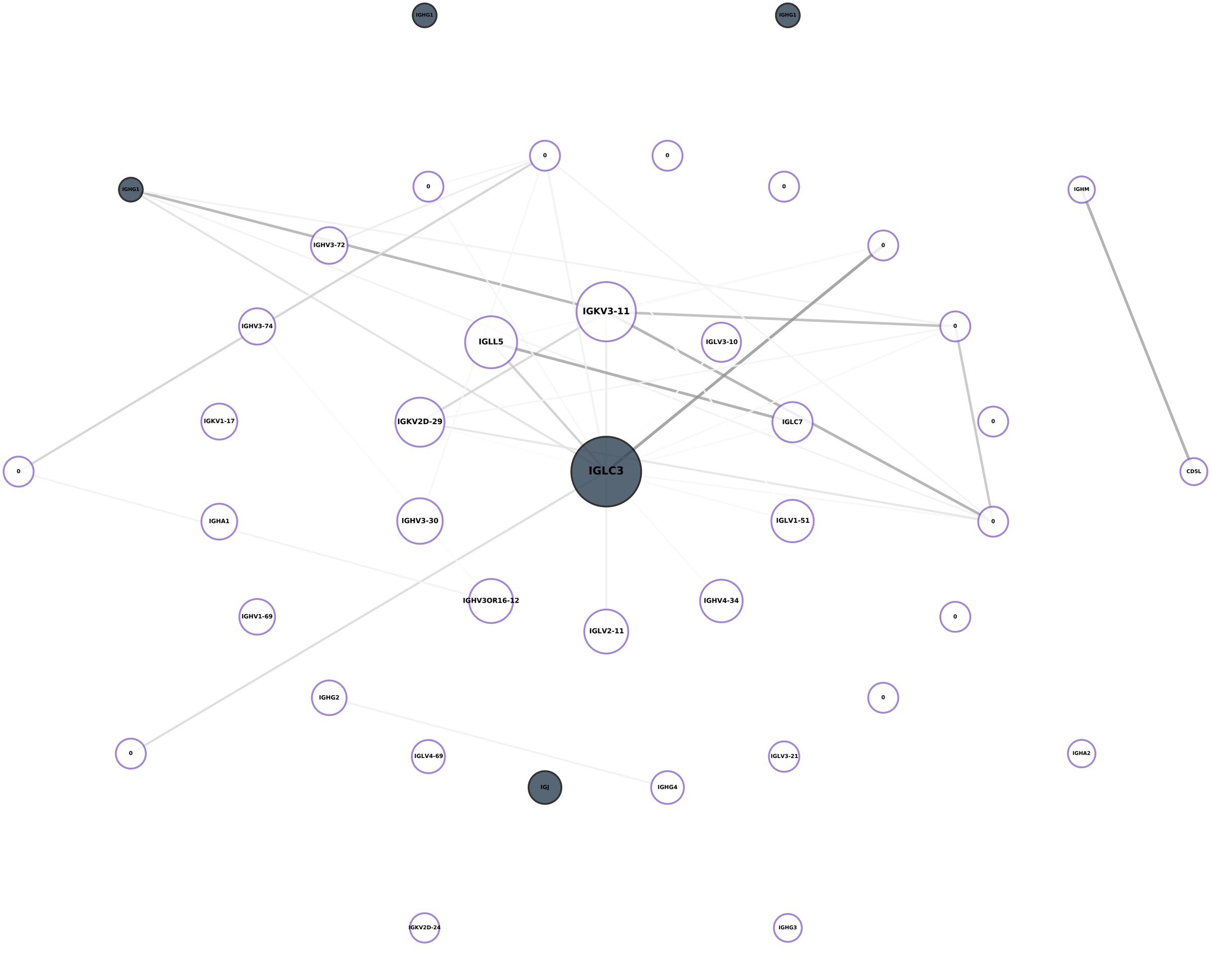
Module 38, n = 53,
FDR Corrected pvalue 0.00025693



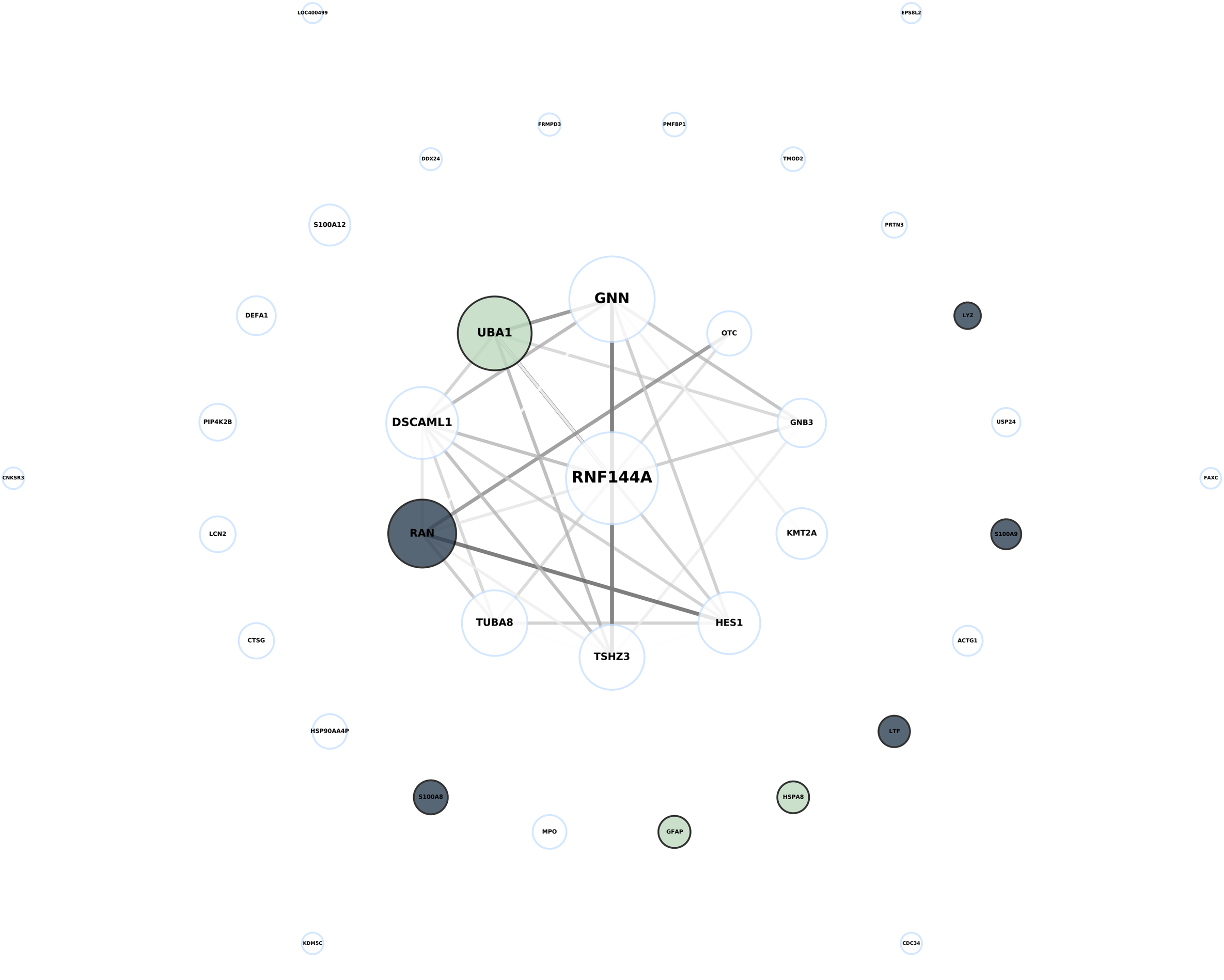
Module 39, n = 48,
FDR Corrected pvalue 0.96802



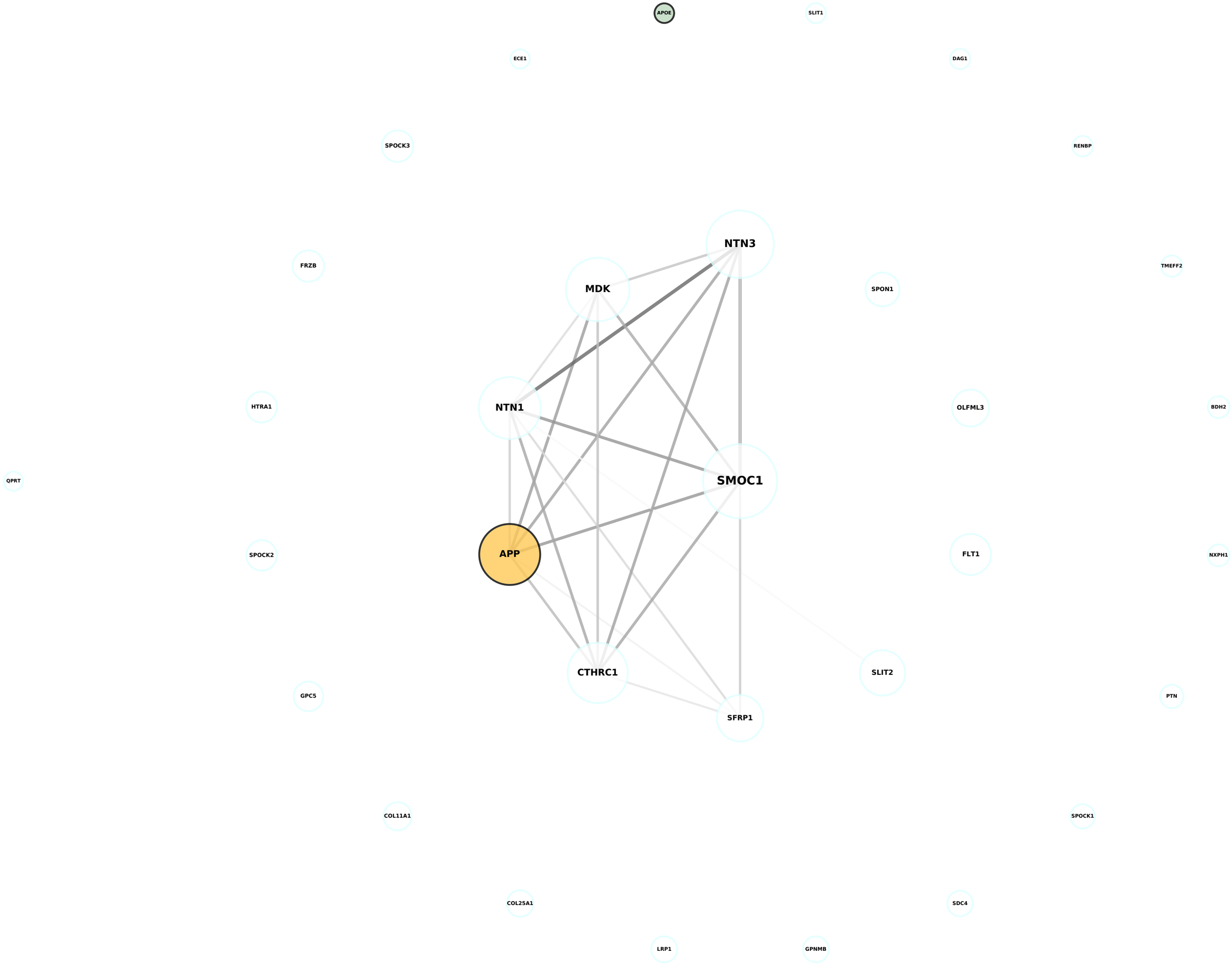
Module 40, n = 41,
FDR Corrected pvalue 0.49975



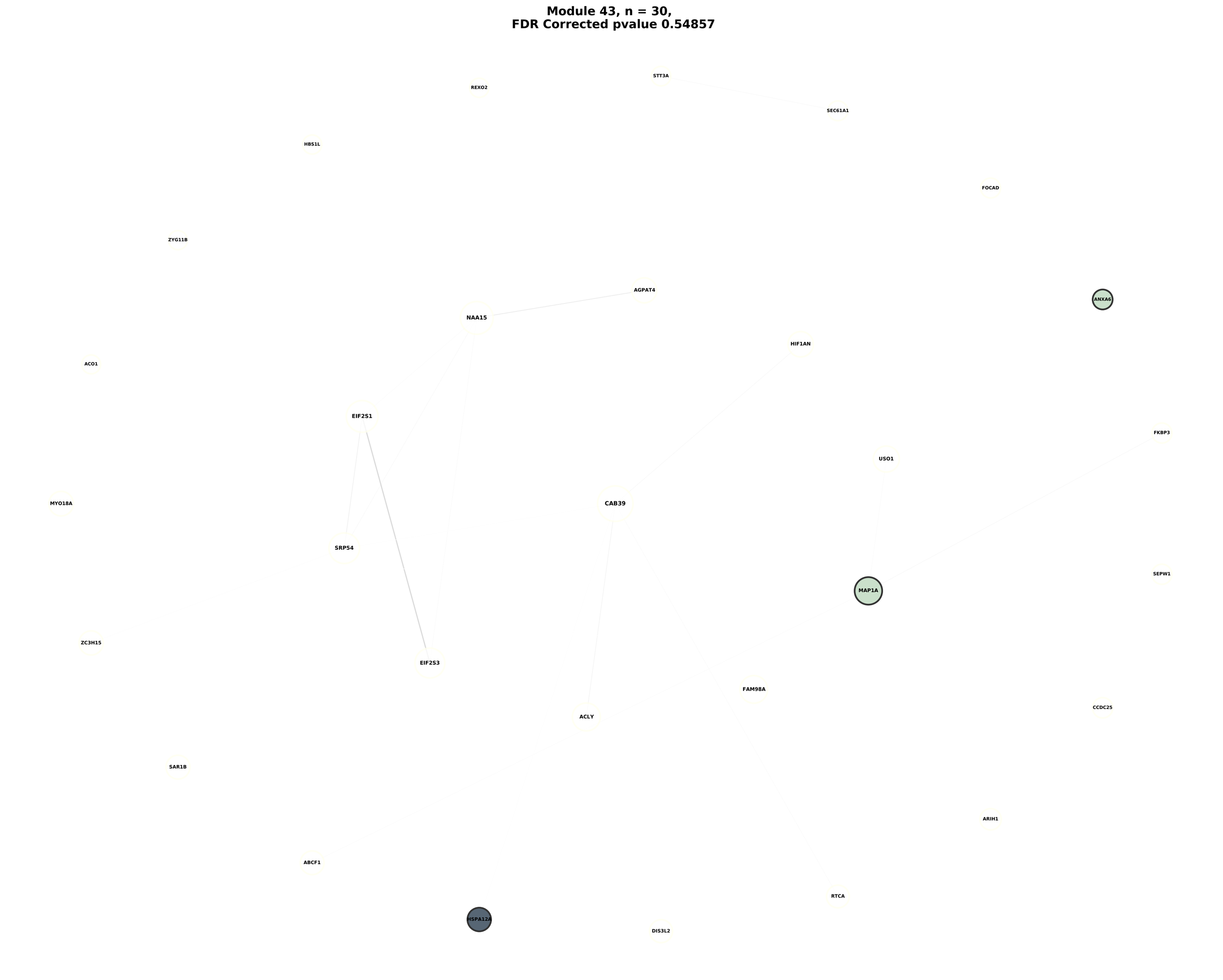
Module 41, n = 37,
FDR Corrected pvalue 0.0064004



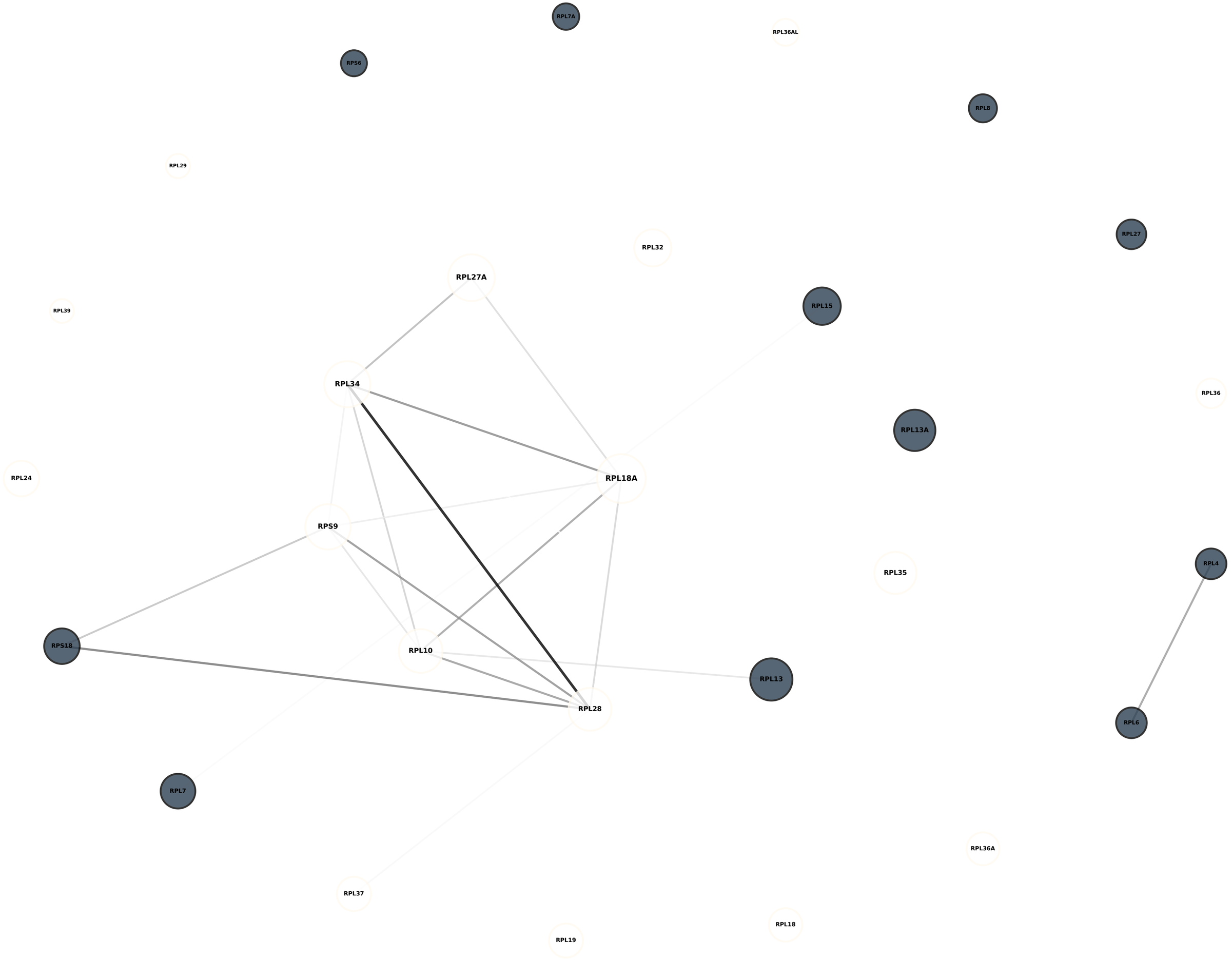
Module 42, n = 32,
FDR Corrected pvalue 1



Module 43, n = 30,
FDR Corrected pvalue 0.54857



Module 44, n = 28,
FDR Corrected pvalue 2.3129e-06



GO Analysis on TMT AD Network Modules. Gene ontology (GO) analysis was performed to gain insight into the biological meaning of each AD protein network module. Enrichment for a given ontology is shown by *z* score.

TMT AD Network Module Eigenprotein Levels. *n*=106 control, 200 AsymAD, 182 AD. Differences among case groups were assessed by one-way ANOVA with Tukey test. Boxplots represent the median, 25th, and 75th percentiles, and box hinges represent the interquartile range of the two middle quartiles within a group. Datapoints up to 1.5 times the interquartile range from box hinge define the extent of whiskers (error bars).

TMT AD Network Module Protein Graphs and Overlap with Amyloid-β Plaque and Tau Neurofibrillary Tangle Proteins. The size of each circle indicates the relative eigenprotein correlation value (kME) in each network module. Those proteins with the largest kME are considered “hub” proteins within the module, and explain the largest variance in module expression. Lines represent weighted adjacency values between proteins. Proteins colored orange are consistently found associated with amyloid-β plaques. Proteins colored dark blue are found to be associated with tau neurofibrillary tangles (NFTs). Proteins colored green are found to be associated with both plaques and tangles.