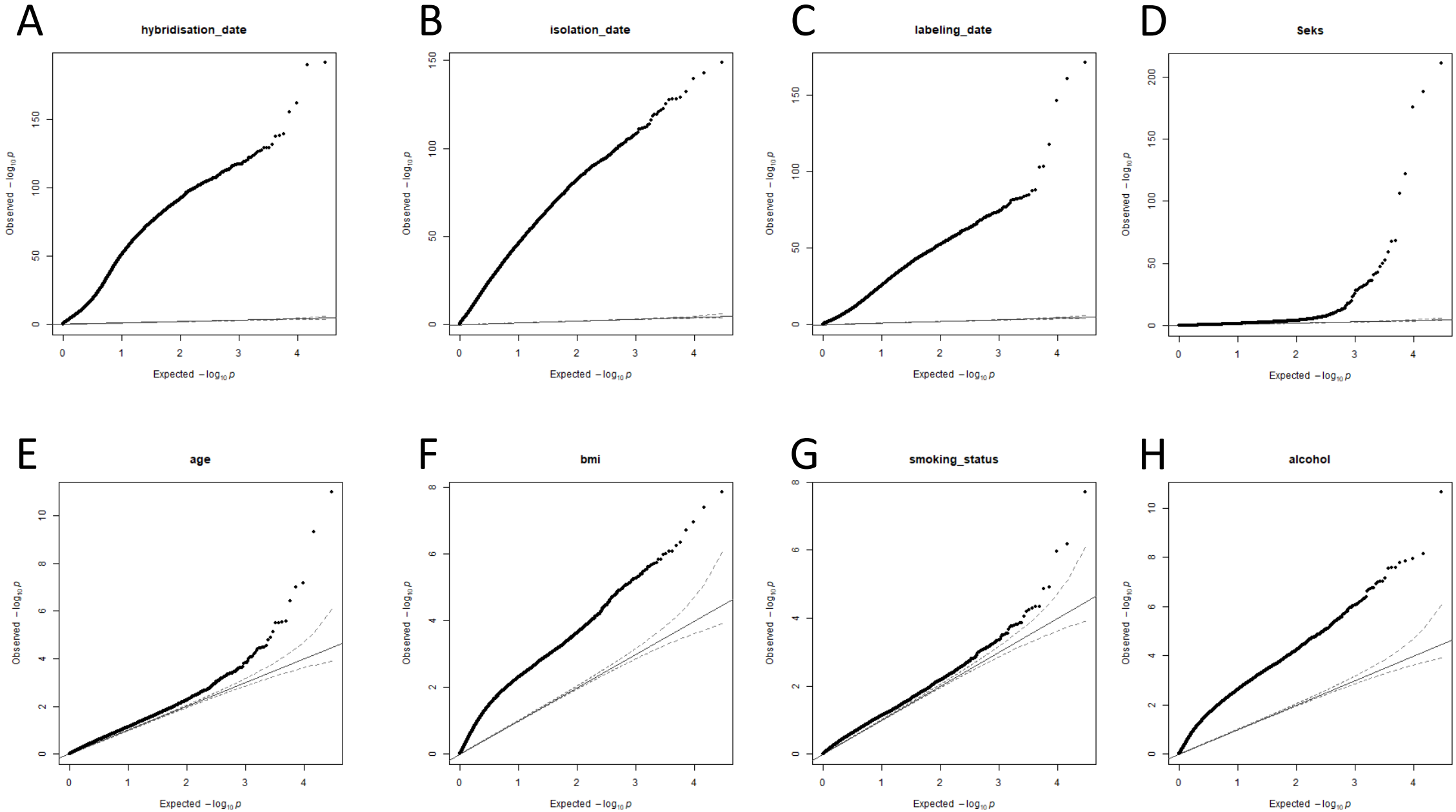
Supplementary Figures S1

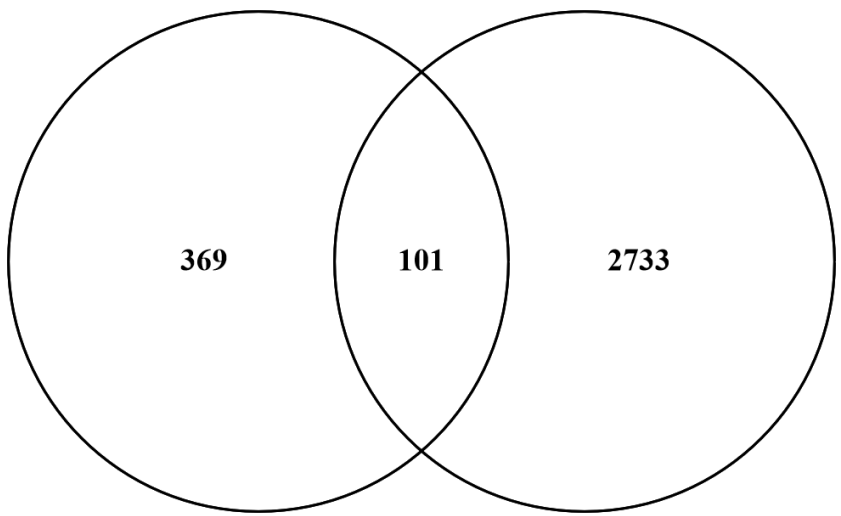
ppq plot of covariates included in the final models. The ppq plots visualize the distribution of p-values from a anova test when comparing the regression model with and without the respective covariate.


A
hybridisation_date
B
isolation_date
C
labeling_date
D
Seks
E
age
F
bmi
G
smoking_status
H
alcohol
Observed $-\log_{10} p$
Expected $-\log_{10} p$

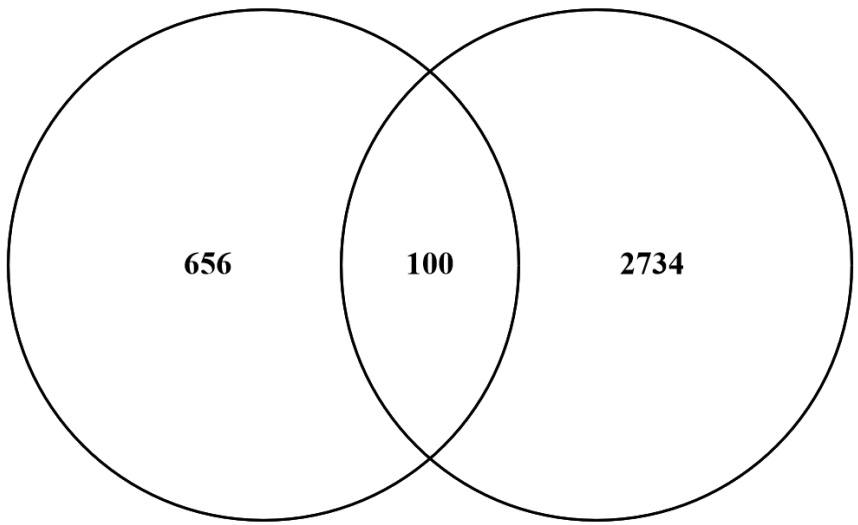
Supplementary Figures S2

Overlap of Cd associated genes in males with two recent AD publication. The Venn diagramm show the overlap with the genetic meta-analysis of diagnosed AD patients by Kunkle *et al.,* 2019 (A) and the single cell transcriptomic analysis by Mathys *et al., 2019* (B).

A

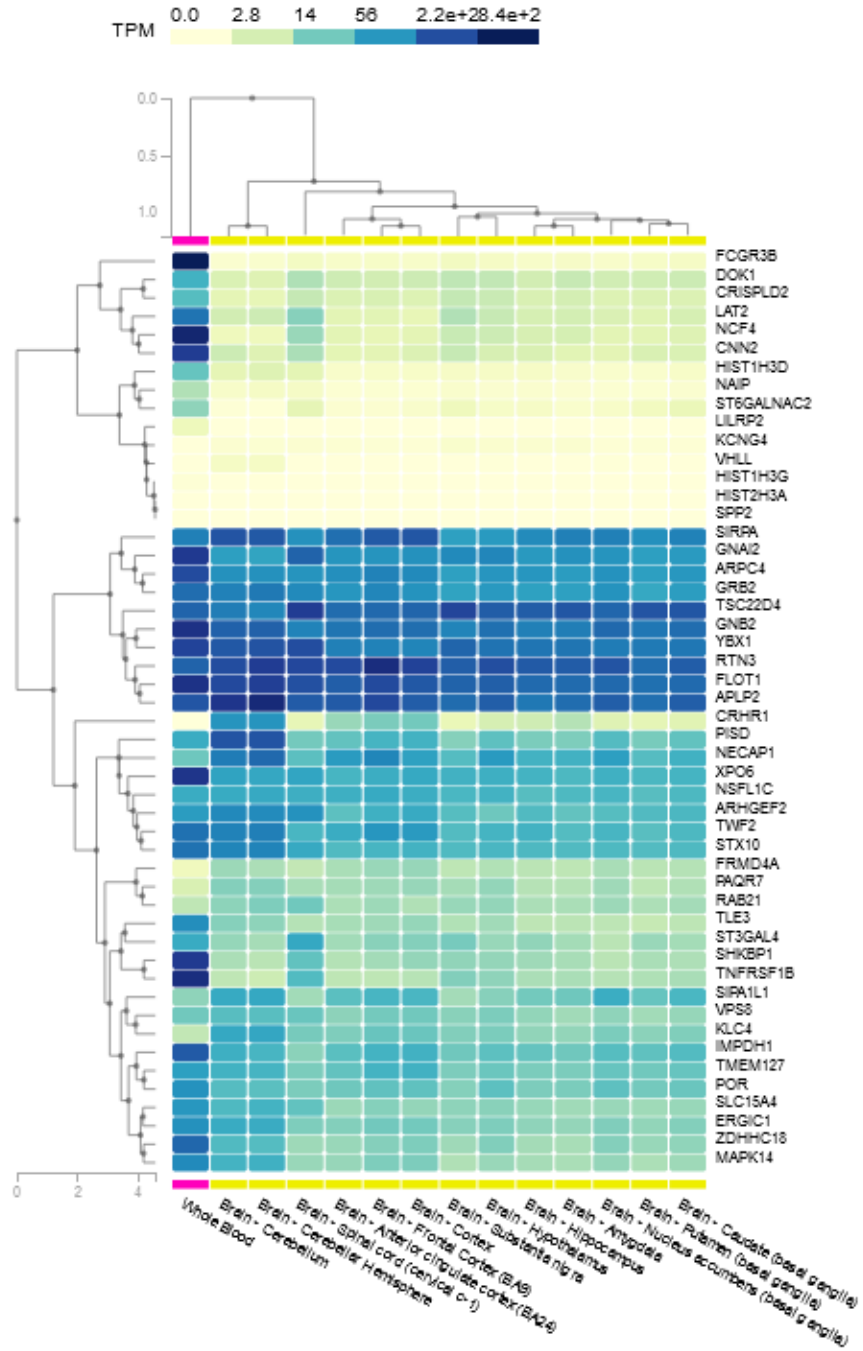

Kunkle et al
Cd assoc. males
369
101
2733

B


Mathys et al
Cd assoc. males
656
100
2734

Supplementary Figures S3

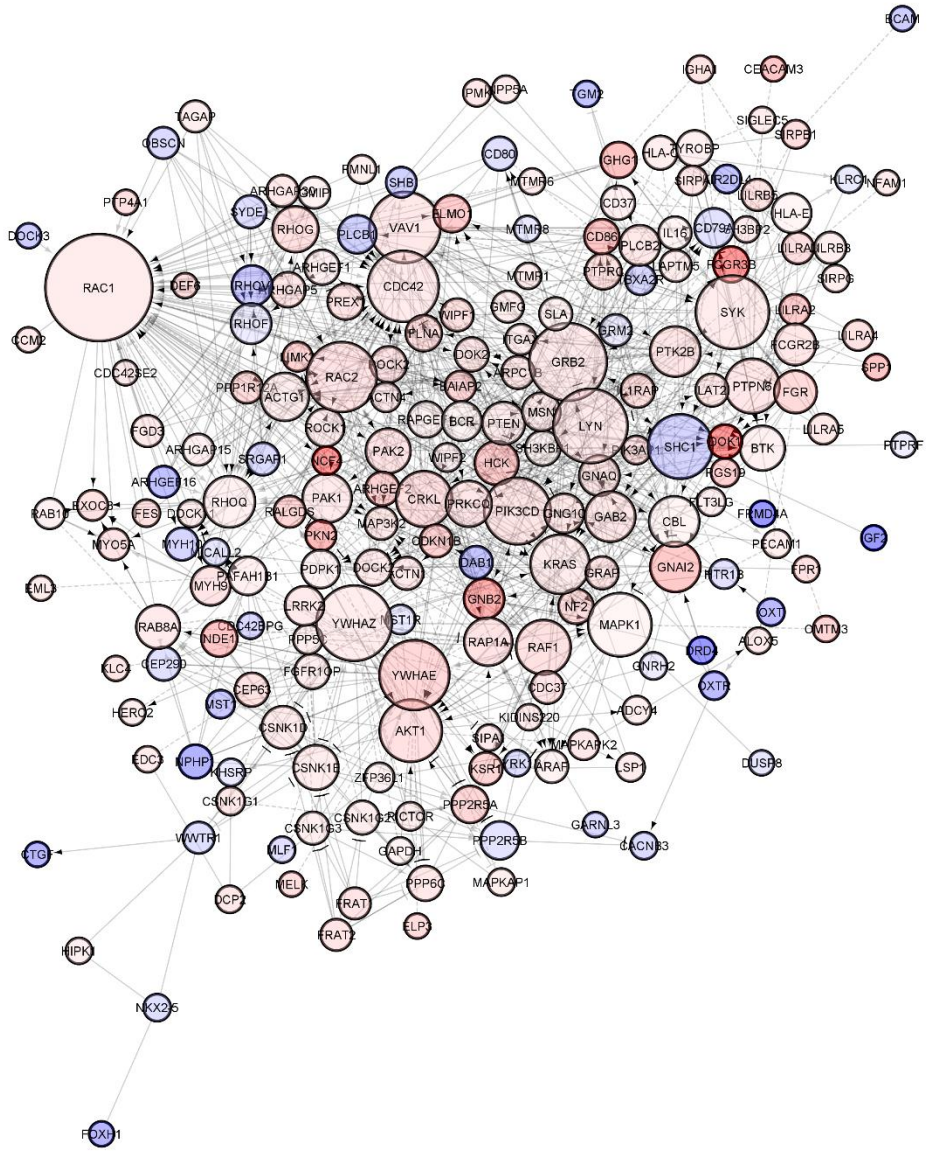
Expression of top 50 significant Cd associated genes in males across brain samples. The heatmap shows the expression in transcripts per million (TPM) for the top 50 genes ranked by significance across whole blood and multiple brain regions derived from the GTEx database (version 8) The data shows that the lage majority of genes identified in blood are similarly expressed across all brain tissue.


TPM
0.0
2.8
14
56
2.2e+28.4e+2
FCGR3B
DOK1
CRISPLD2
LAT2
NCF4
CNN2
HIST1H3D
NAIP
ST6GALNAC2
LILRP2
KCNG4
VHLL
HIST1H3G
HIST2H3A
SPP2
SIRPA
GNAI2
ARPC4
GRB2
TSC22D4
GNB2
YBX1
RTN3
FLOT1
APLP2
CRHR1
PISD
NECAP1
XPO6
NSFL1C
ARHGEF2
TWF2
STX10
FRMD4A
PAQR7
RAB21
TLE3
ST3GAL4
SHKBP1
TNFRSF1B
SIPA1L1
VPS8
KLC4
IMPDH1
TMEM127
POR
SLC15A4
ERGIC1
ZDHHC18
MAPK14
Whole Blood
Brain - Cerebellum
Brain - Cerebellar Hemisphere
Brain - Spinal cord (cervical c-1)
Brain - Anterior cingulate cortex (BA24)
Brain - Frontal Cortex (BA9)
Brain - Cortex
Brain - Substantia nigra
Brain - Hypothalamus
Brain - Hippocampus
Brain - Amygdala
Brain - Nucleus accumbens (basal ganglia)
Brain - Putamen (basal ganglia)
Brain - Caudate (basal ganglia)

Supplementary Figures S4

PPI network of Cd associated genes in males. The network was obtained from Reactome FIs using Cytoscape. To enable readability of this large network we applied MCL Cluster and only selected for clusters with a minimum of 40 connected nodes. This resulted in 8 subnetworks (A-H). Node sizes indicate the degree. Color indicates a calculated GeneScore derived from the multiplication of the β-coefficient and $-\log_{10}$(pvalue). A red shade indicates a significant positive, a blue shade a significant negative association of the respective transcript with Cd exposure in men.

A


GeneScore
-1
1
RAC1
CDC42
VAV1
RHOG
RHOQ
RHOF
RAC2
PAK1
PAK2
CRKL
PIK3CD
GRB2
LYN
SYK
SHC1
BTK
PTPN6
FGR
PTK2B
KRAS
RAF1
MAPK1
AKT1
YWHAZ
YWHAE
GNB2
GNAQ
GNAI2
GAB2
CBL
LAT2
LCP2
PLCB2
PLCG2
ITGA2
ITGB2
SLA
SLA2
LILRA2
LILRB1
LILRB2
LILRB3
LILRA4
LILRA5
FCGR2B
FCGR3B
SIRPB1
SIRPG
CD37
CD80
CD86
HLA-E
HLA-DRB1
HLA-DQB1
IL16
CD79A
CD79B
TYROBP
TREM2
SIGLEC5
CEACAM3
CEACAM1
PECAM1
FRMD4A
PTPRF
SPP1
GPR183
FLT3LG
HTR1B
OXTR
ADCY4
DRD4
ALOX5
OMTN3
GNRH2
FPR1
GPR65
DUSP8
MAPKAPK2
MAPKAP1
RICTOR
MTOR
GSK3B
PPP2R5A
PPP2R5B
PPP6C
GAPDH
CSNK1G1
CSNK1G2
CSNK1G3
CSNK1E
CSNK1D
ZFP36L1
KSR1
ARAF
ERK1
SPY1
KIDINS220
SIPA1
EDC3
DCP2
DDX6
LSM14A
EIF4E
EIF4G3
EIF4A2
PABPC1
UPF1
SMG1
SMG5
SMG7
NCBP1
NCBP2
WTAP
METTL3
METTL14
ZC3H13
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RBM15B
VIRMA
CBLL1
HAKAI
YTHDF1
YTHDF2
YTHDF3
YTHDC1
YTHDC2
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ALKBH5
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HNRNPA2B1
IGF2BP1
IGF2BP2
IGF2BP3
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LRPPRC
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RBMX
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IGF2BP3
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ELMO1
ELMO2
ELMO3
DEF6
SWAP70
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PREX2
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TIAM2
VAV2
VAV3
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ARHGEF9
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ARHGEF18
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ARHGAP35
ARHGAP45
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PIK3R5
PIK3R6
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PIK3CG
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GPR999
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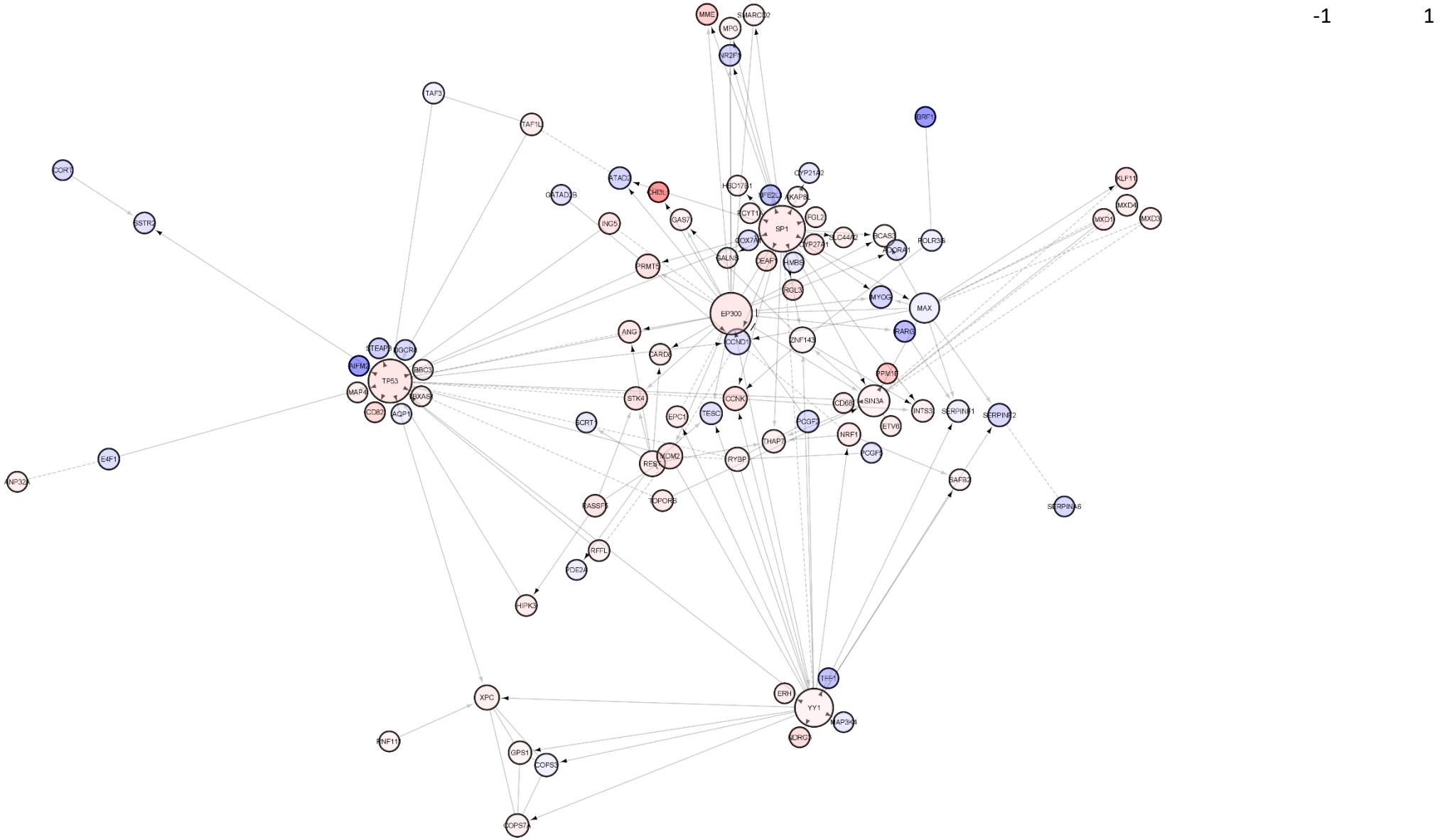
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NR2F1
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TAF1L
BRF1
CORT
SSTR2
ATAD2
CHI3L1
GATAD2B
ING5
GAS7
HSD17B1
CYP21A2
IFE2L1
AKAP8L
FCYT1A
SP1
FGL2
COX7A1
CYP27A1
SLC44A2
BCAS3
ADORA1
POLR3G
KLF11
MXD4
MXD1
MXD3
PRMT5
GALNS
DEAF1
HMBS
RGL3
MYOG
MAX
EP300
ANG
CCND1
ZNF143
RARG
CARD8
STEAP3
DGCR8
AIFM2
TP53
BBC3
MAP4
TBXAS1
CD82
AQP1
STK4
CCNK
CD68
SIN3A
PPM1B
INTS3
SERPINF1
SERPINF2
ETV6
EPC1
TESC
PCGF2
NRF1
THAP7
PCGF5
SCRT1
MDM2
RESTL
RYBP
E4F1
ANP32A
SAFB2
SERPINA6
RASSF5
TOPORS
RFFL
PDE2A
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GPS1
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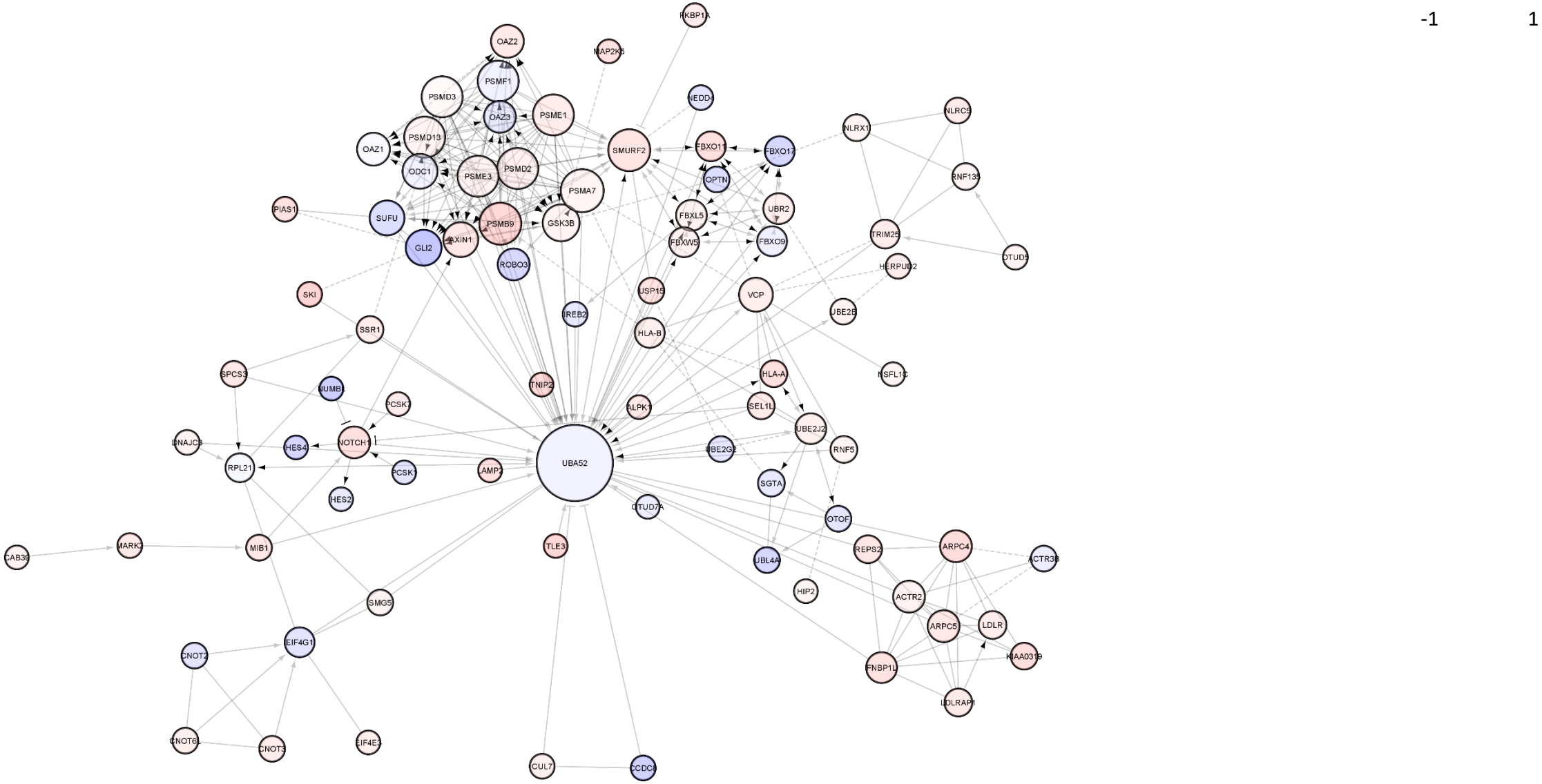
COPS7A

C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MAP2K5
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NEDD4
OAZ3
PSME1
NLRC5
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PSMD13
OAZ1
SMURF2
FBXO11
FBXO17
ODC1
PSME3
PSMD2
OPTN
RNF135
PSMA7
PIAS1
SUFU
FBXL5
UBR2
PSMB9
GSK3B
AXIN1
FBXW5
FBXO9
TRIM25
GLI2
ROBO3
DTUD3
HERPUD2
SKI
USP15
VCP
TREB2
UBE2E
SSR1
HLA-B
SPCS3
NSFL1C
HLA-A
NUMB
TNIP2
PCSK7
ALPK1
SEL1L
UBE2J2
DNAJC3
HES4
NOTCH1
UBE2G2
RNF5
RPL21
PCSK5
AMP2
UBA52
SGTA
HES2
OTUD7A
OTOF
CAB39
MARK2
MIB1
TLE3
REPS2
ARPC4
ACTR3B
UBL4A
HIP2
SMG5
ACTR2
ARPC5
LDLR
EIF4G1
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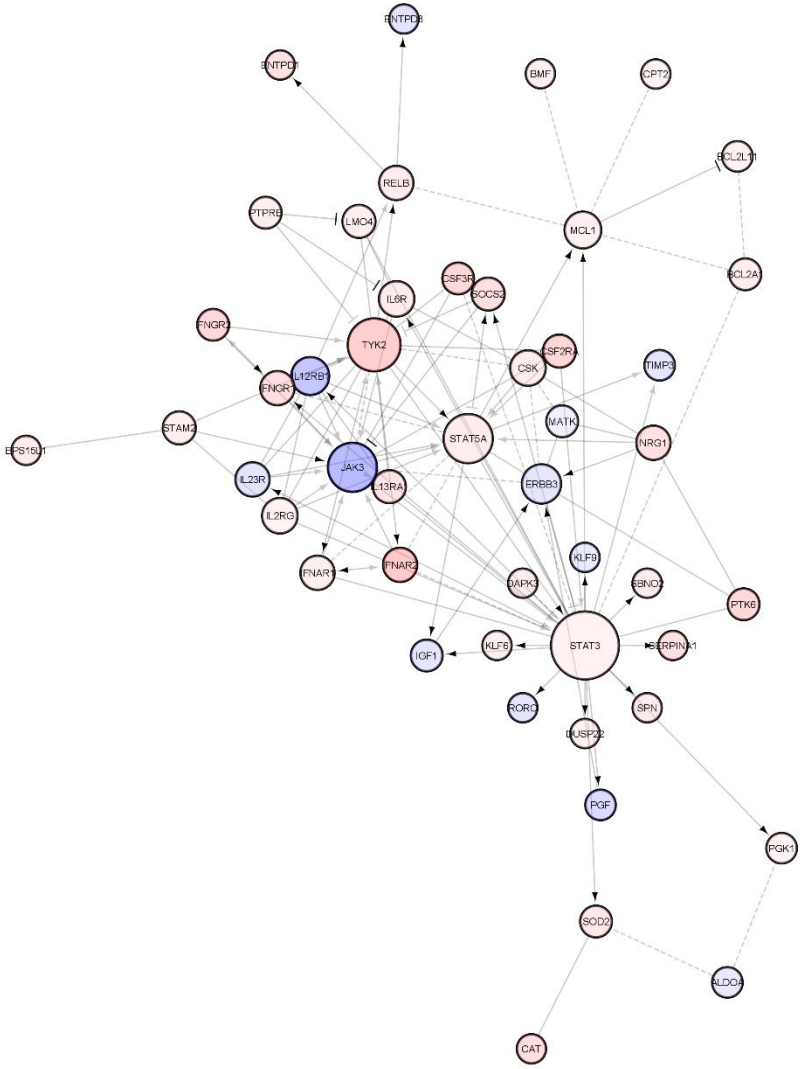
CUL7
CCDC8

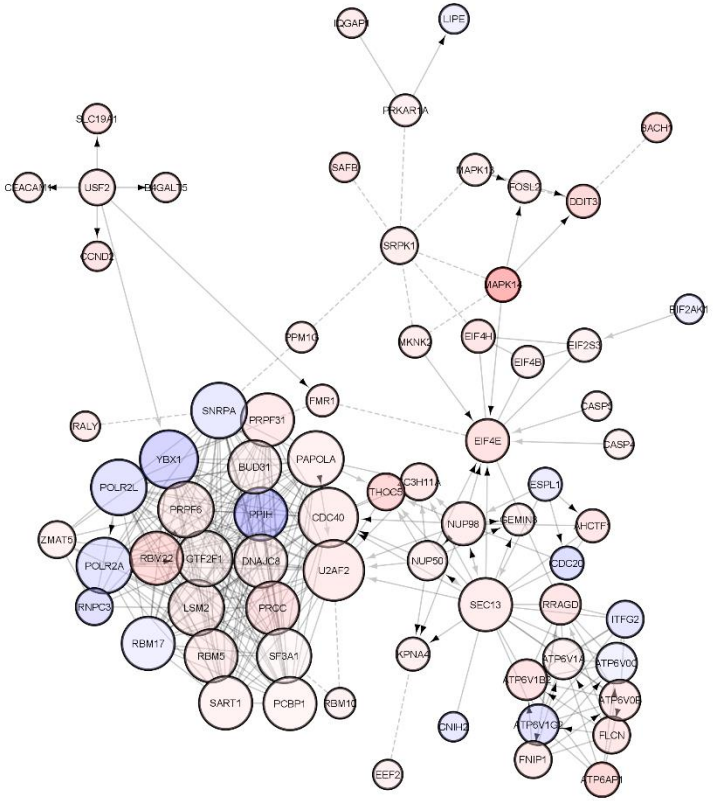
D



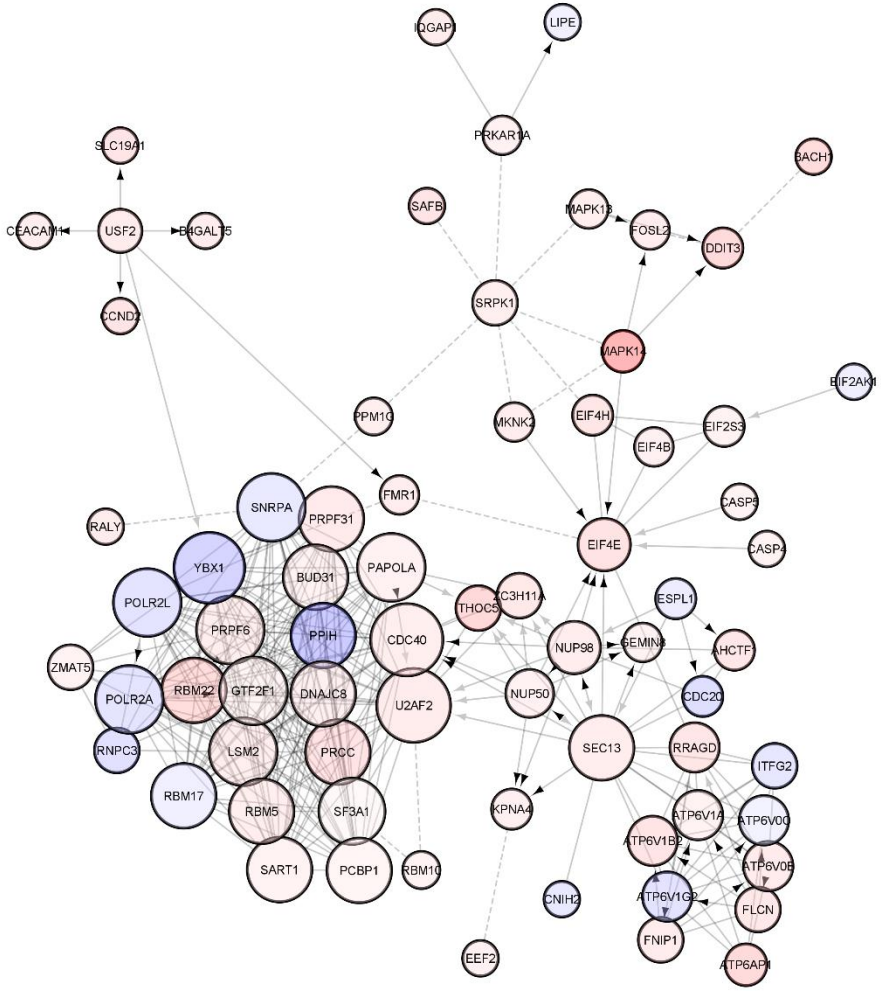
E

GeneScore

-1 1



F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LIPE
PRKAR1A
SLC19A1
BACH1
SAFB
MAPK13
FOSL2
DDIT3
CEACAM1
USF2
B4GALT5
SRPK1
CCND2
MAPK14
EIF2AK1
PPM1G
MKNK2
EIF4H
EIF2S3
EIF4B
FMR1
SNRPA
PRPF31
CASP8
RALY
EIF4E
CASP4
YBX1
BUD31
PAPOLA
ZC3H11A
THOC5
ESPL1
POLR2L
PRPF6
PPIH
CDC40
NUP98
GEMIN4
AHCTF1
ZMAT5
POLR2A
RBM22
GTF2F1
DNAJC8
U2AF2
NUP50
CDC20
RNPC3
LSM2
PRCC
SEC13
RRAGD
ITFG2
RBM17
RBM5
SF3A1
KPNA4
ATP6V1A
ATP6V0C
ATP6V1B2
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PCBP1
RBM10
CNIH2
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FLCN
FNIP1
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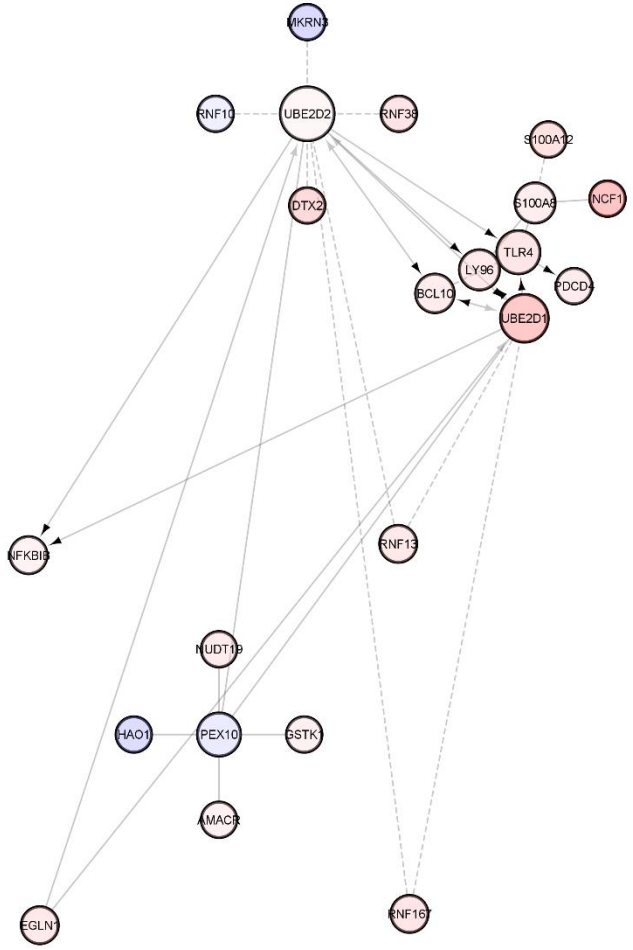
ATP6AP1

G


MKRN3
RNF10
UBE2D2
RNF38
S100A12
DTX2
S100A8
NCF1
TLR4
LY96
BCL10
PDCD4
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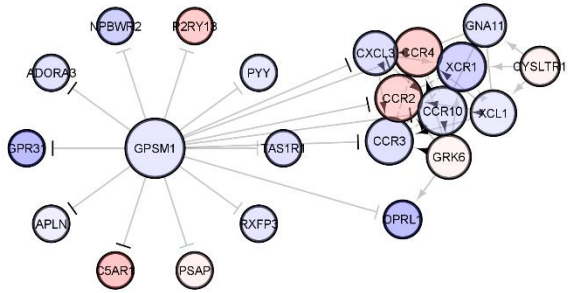
NFKBIB
RNF13
NUDT19
HAO1
PEX10
GSTK1
AMACR
EGLN1
RNF167

H


GeneScore
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P2RY13
GNA11
ADORA3
PYY
CXCL3
CCR4
XCR1
GPR31
GPSM1
TAS1R1
CCR2
CCR10
XCL1
CCR3
GRK6
APLN
RXFP3
DPRL1
C5AR1
PSAP