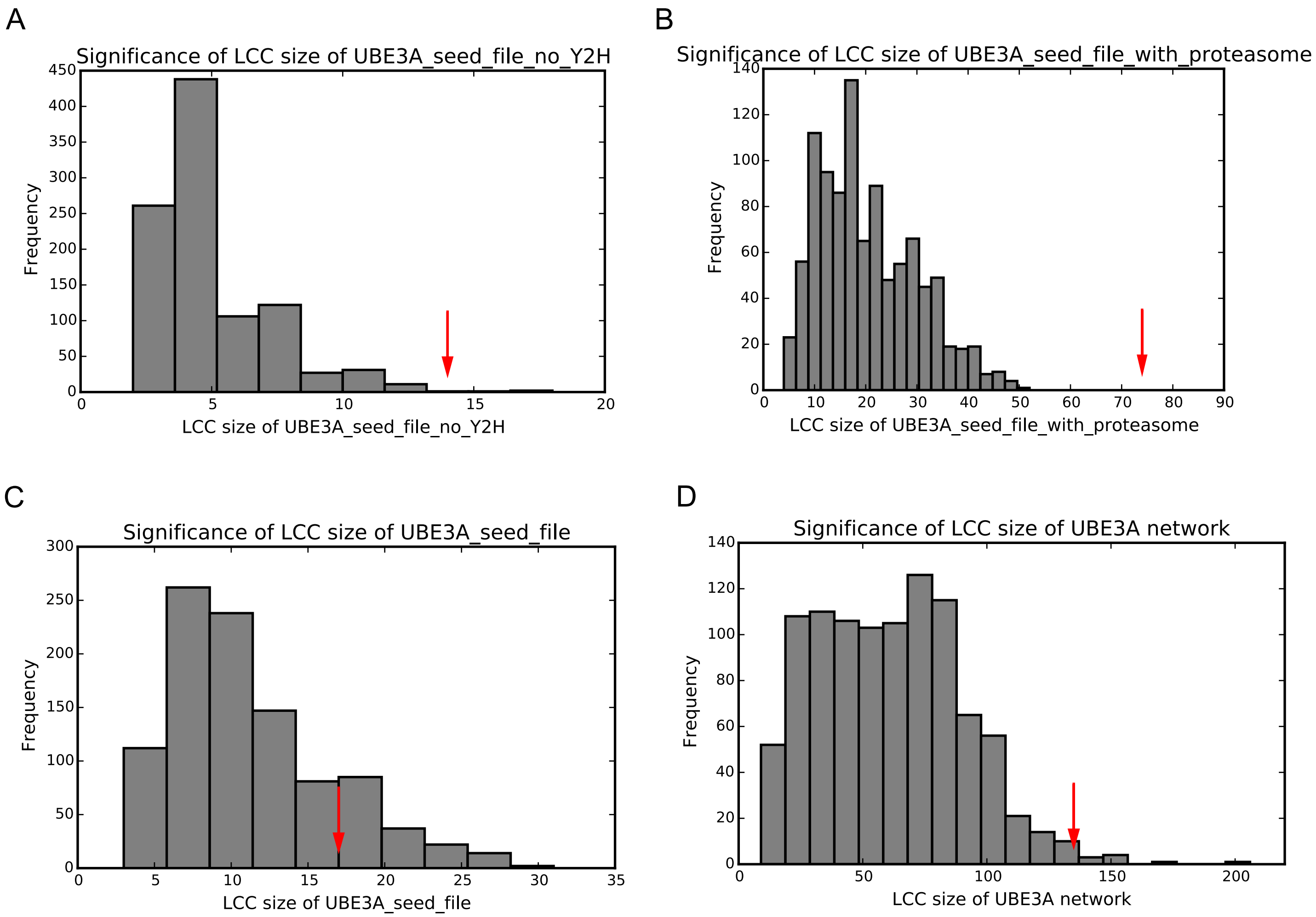
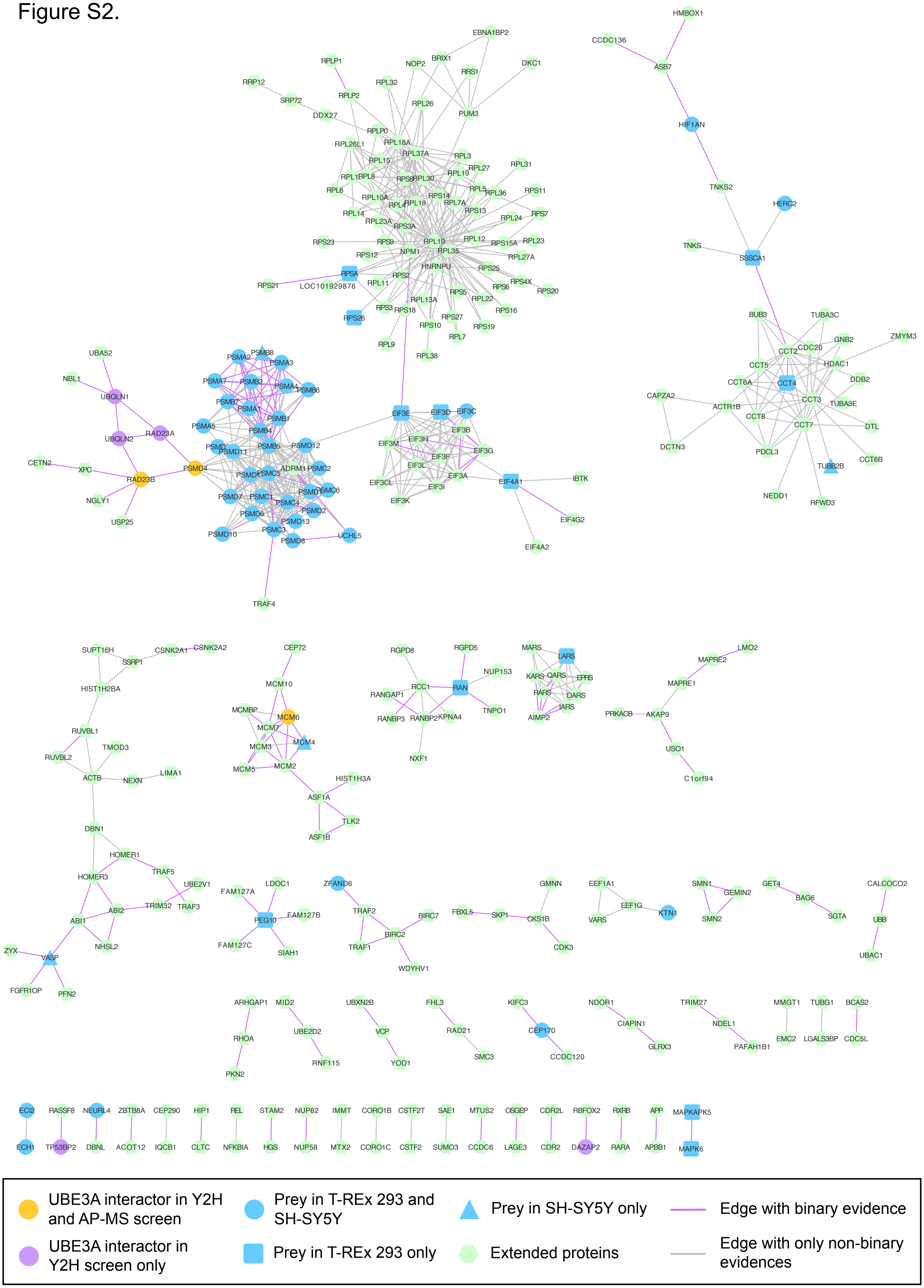


Figure S1. Significances of closeness in QBCHL of different sets of UBE3A interactors. Significance of closeness were calculated by comparing the largest connected component (LCC) formed by a given set of query proteins in the QBCHL network to the LCC formed by these query proteins in 1000 degree-controlled randomized QBCHL networks. A: UBE3A interactors as identified in the AP-MS screens without the proteasome subunits. B: UBE3A interactors as identified in the AP-MS screens with the proteasome subunits. C: Union of UBE3A interactors identified in the AP-MS screens or Y2H screens. D: LCC of network formed around UBE3A using QBCHL. The corresponding lists of query proteins can be found on GitHub.

Figure S2.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CCDC136
ASB7
HIF1AN
TNKS2
HERC2
TNKS
SSSCA1
EBNA1BP2
BRIX1
NOP2
DKC1
RRS1
RPLP1
RPL32
RRP12
RPLP2
RPL26
SRP72
PUM3
DDX27
RPLP0
RPL26L1
RPL18A
RPL37A
RPL15
RPL3
RPL27
RPL31
RPL1
RPL8
RPS8
RPL30
RPL19
RPL5
RPL36
RPS11
RPL6
RPL10A
RPS14
RPL4
RPL18
RPL7A
RPS13
RPL14
RPL24
RPS7
RPL23A
RPS3A
RPS23
RPS9
RPL10
RPL12
RPS15A
RPL23
RPS12
NPM1
RPL35
RPL27A
RPSA
RPS2
HNRNPU
RPS25
RPS21
LOC101929876
RPL11
RPS6
RPS4X
RPS20
RPL13A
RPS5
RPL22
RPS3
RPS18
RPS16
RPS26
RPS27
RPS10
RPS19
RPL9
RPL7
RPL38
BUB3
TUBA3C
ZMYM3
GNB2
CCT2
CDC20
CCT5
HDAC1
DDB2
CAPZA2
CCT6A
CCT4
ACTR1B
CCT3
TUBA3E
CCT8
CCT7
DTL
DCTN3
PDCL3
TUBB2B
CCT6B
NEDD1
RFWD3
UBA52
PSMB8
PSMA2
PSMA3
NBL1
PSMA7
PSMB2
PSMA4
PSMB6
UBQLN1
PSMB7
PSMA1
PSMB1
PSMA5
UBQLN2
RAD23A
PSMB4
PSMD3
PSMD11
PSMB5
PSMD12
CETN2
XPC
PSMD4
ADRM1
PSMC2
RAD23B
PSMD1
PSMC5
PSMD14
PSMC6
NGLY1
PSMD7
PSMC1
PSMC4
PSMD6
PSMD2
USP25
PSMD13
PSMD10
PSMC3
UCHL5
PSMD8
TRAF4
EIF3E
EIF3D
EIF3C
EIF3B
EIF3M
EIF3H
EIF3F
EIF3G
EIF3L
EIF3CL
EIF3A
EIF4A1
IBTK
EIF3I
EIF3K
EIF4G2
EIF4A2
SUPT16H
CSNK2A1
CSNK2A2
SSRP1
HIST1H2BA
RUVBL1
TMOD3
RUVBL2
ACTB
NEXN
LIMA1
DBN1
HOMER1
TRAF5
HOMER3
UBE2V1
ABI2
TRIM32
TRAF3
ABI1
NHSL2
ZYX
VASP
FGFR1OP
PFN2
CEP72
MCM10
MCMBP
MCM6
MCM7
MCM4
MCM3
MCM5
MCM2
HIST1H3A
ASF1A
TLK2
ASF1B
RGPD8
RGPD5
NUP153
RCC1
RAN
RANGAP1
TNPO1
RANBP3
RANBP2
KPNA4
NXF1
MARS
LARS
KARS
QARS
EPRS
RARS
DARS
IARS
AIMP2
LMO2
MAPRE2
MAPRE1
PRKACB
AKAP9
USO1
C1orf94
FAM127A
LDOC1
ZFAND6
PEG10
FAM127B
FAM127C
SIAH1
TRAF2
BIRC7
BIRC2
TRAF1
WDYHV1
FBXL5
SKP1
GMNN
CKS1B
CDK3
EEF1A1
EEF1G
VARS
KTN1
SMN1
GEMIN2
SMN2
GET4
BAG6
SGTA
CALCOCO2
UBB
UBAC1
ARHGAP1
MID2
RHOA
UBE2D2
PKN2
RNF115
UBXN2B
VCP
YOD1
FHL3
RAD21
SMC3
KIFC3
CEP170
CCDC120
NDOR1
CIAPIN1
GLRX3
TRIM27
NDEL1
PAFAH1B1
MMGT1
EMC2
TUBG1
LGALS3BP
BCAS2
CDC5L
ECI2
ECH1
RASSF8
TP53BP2
NEURL4
DBNL
ZBTB8A
ACOT12
CEP290
IQCB1
HIP1
CLTC
REL
NFKBIA
STAM2
HGS
NUP62
NUP58
IMMT
MTX2
CORO1B
CORO1C
CSTF2T
CSTF2
SAE1
SUMO3
MTUS2
CCDC6
OSGEP
LAGE3
CDR2L
CDR2
RBFOX2
DAZAP2
RXRB
RARA
APP
APBB1
MAPKAPK5
MAPK6
UBE3A interactor in Y2H and AP-MS screen
UBE3A interactor in Y2H screen only
Prey in T-REx 293 and SH-SY5Y
Prey in T-REx 293 only
Prey in SH-SY5Y only
Extended proteins
Edge with binary evidence
Edge with only non-binary evidences

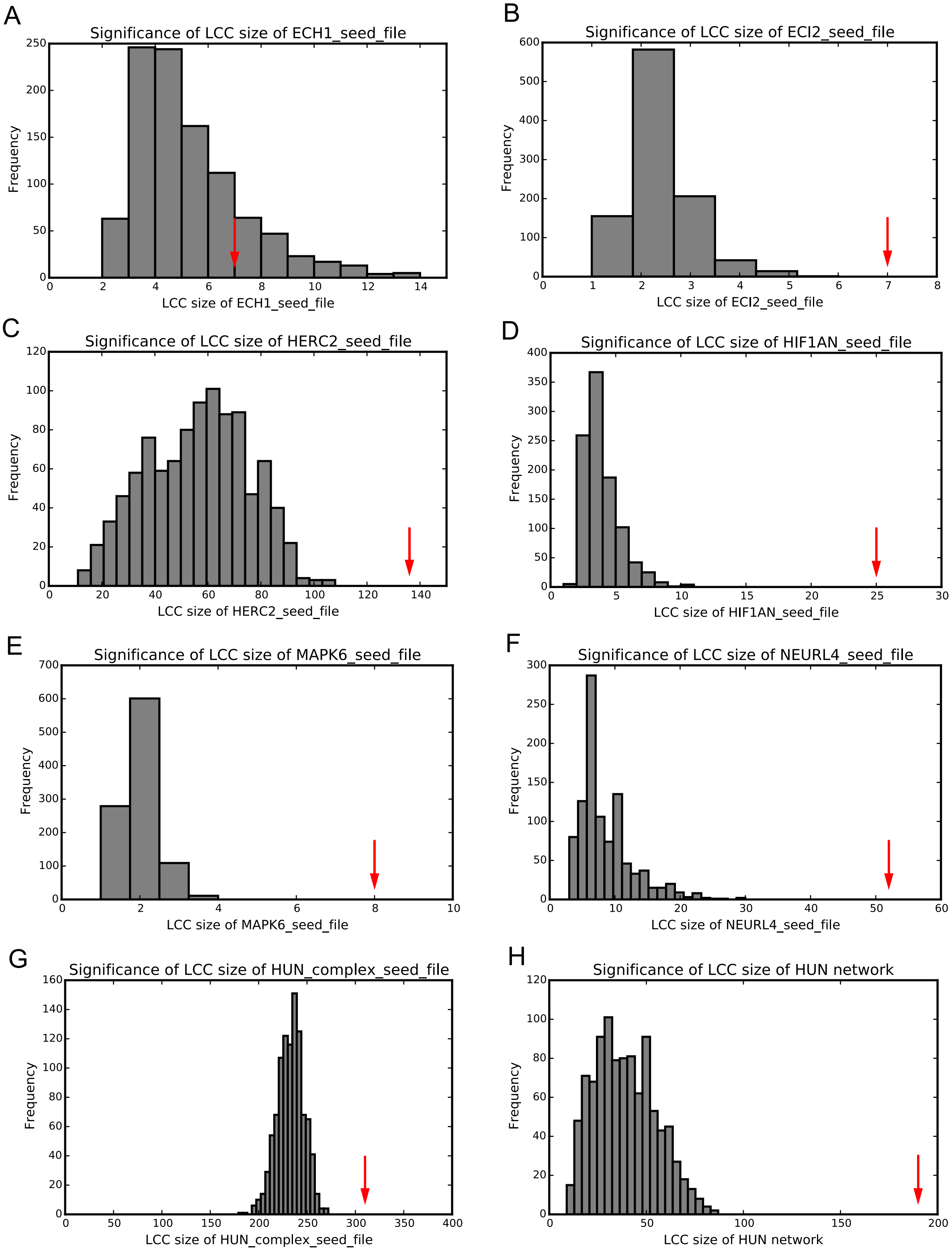
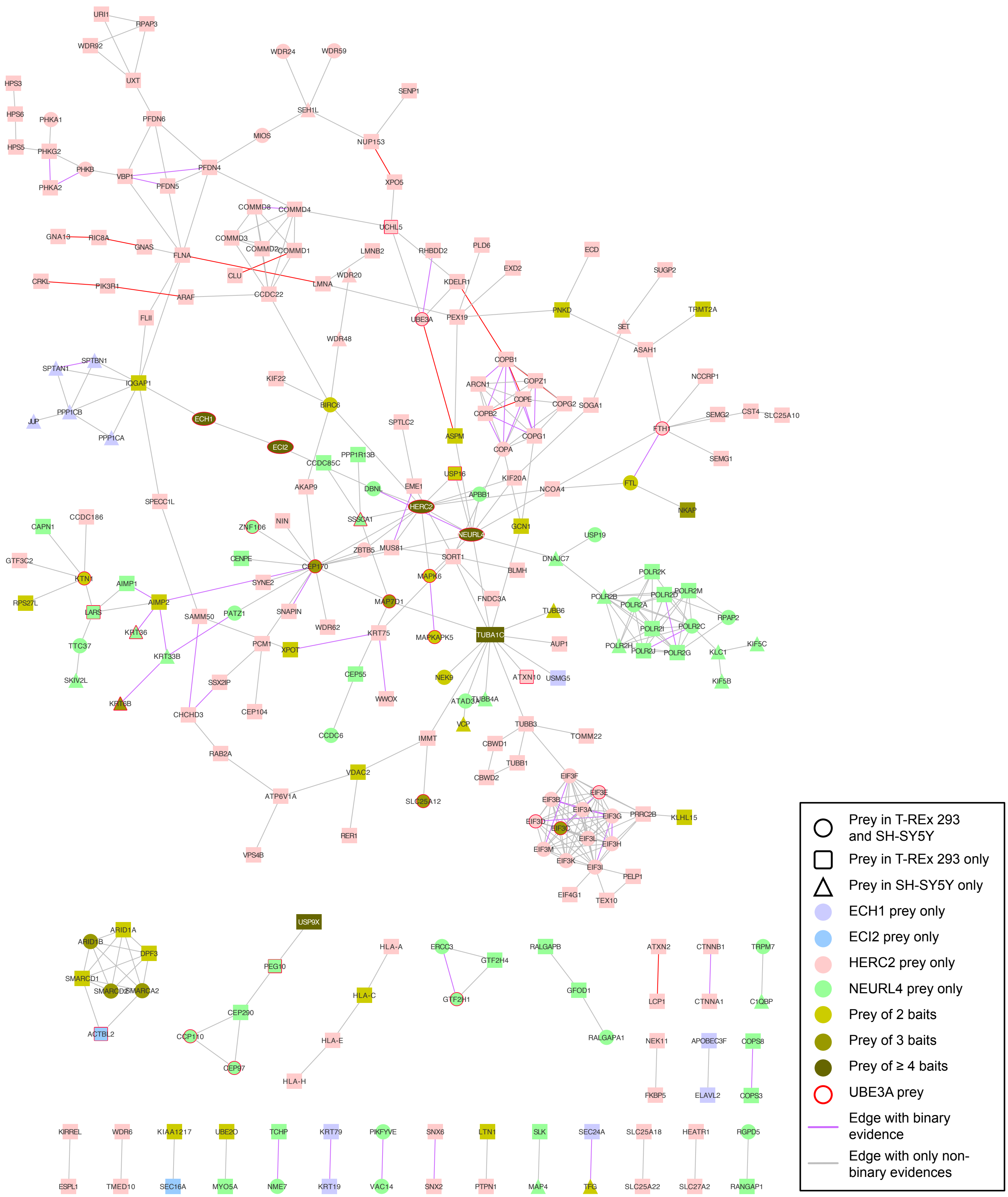
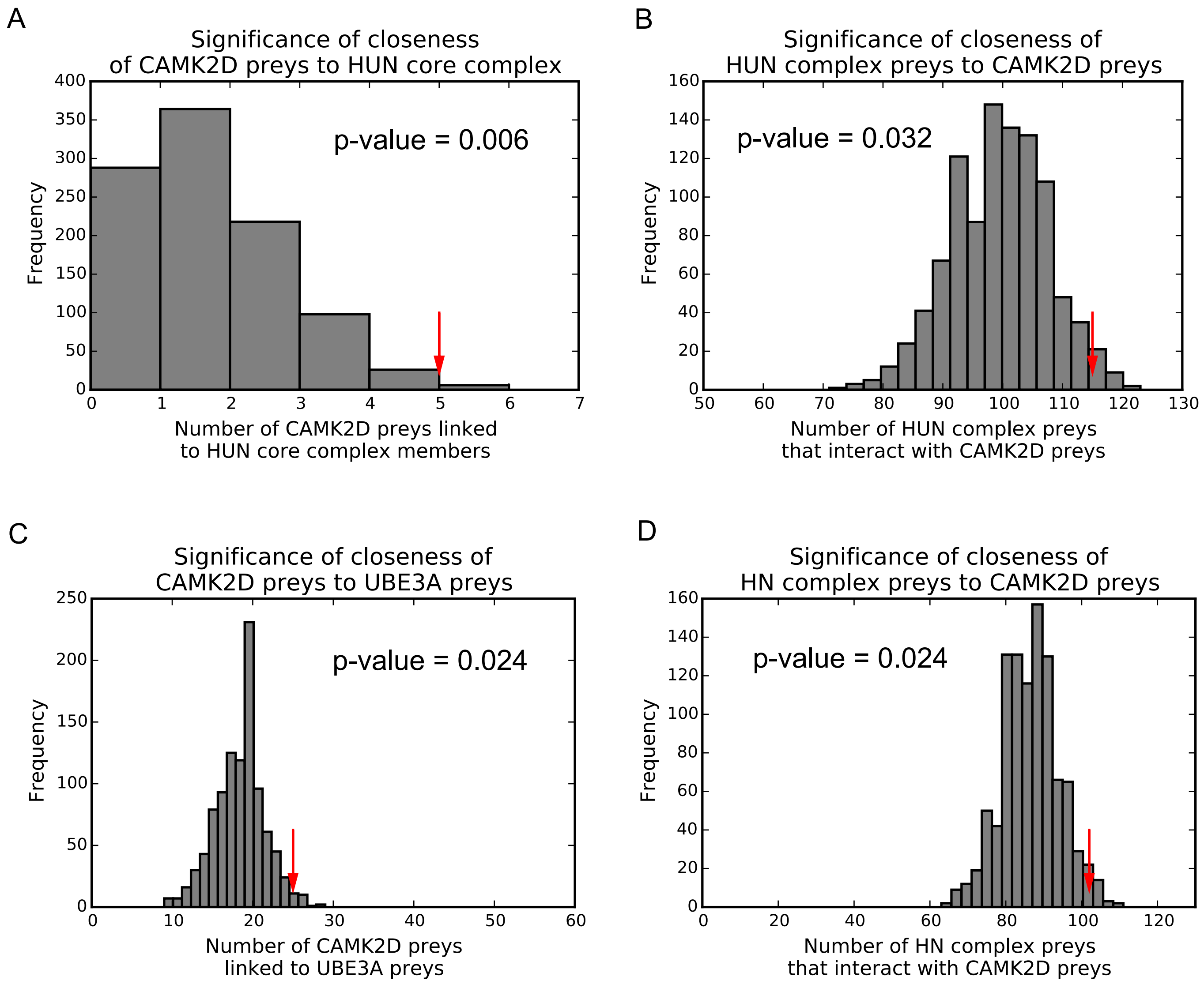


Figure S3. Significances of the size of the largest connected components (LCC) formed by different sets of genes in the QBCHL network. A-F: The set of preys from each individual pulldown were linked to each other using the QBCHL network. The number of preys connected to each other was compared to the number of preys connected when using 1,000 degree-controlled random QBCHL networks. Red arrows indicate the observed number of connected preys using the real network. Grey bars indicate the distribution of numbers of connected preys from the random controls. G: Union of preys from ECH1, ECI2, MAPK6, HERC2, and NEURL4 were tested for the significance of the LCC they form. H: The size of the LCC from the HUN network was tested for its significance.

Figure S4.


URI1
RPAP3
WDR92
UXT
HPS3
HPS6
HPS5
PHKA1
PHKG2
PHKA2
PHKB
VBP1
PFDN6
PFDN5
PFDN4
WDR24
WDR59
SEH1L
MIOS
SENP1
NUP153
XPO5
UCHL5
COMMD8
COMMD4
COMMD3
COMMD2
COMMD1
CLU
CCDC22
GNA13
RIC8A
GNAS
FLNA
CRKL
PIK3R1
ARAF
FLII
LMNB2
LMNA
WDR20
RHBDD2
PLD6
KDELR1
EXD2
ECD
SUGP2
UBE3A
PEX19
PNKD
SET
TRMT2A
ASAH1
WDR48
SPTAN1
SPTBN1
IQGAP1
JUP
PPP1CB
PPP1CA
KIF22
BIRC6
ECH1
ECI2
COPB1
COPZ1
ARCN1
COPE
COPG2
SOGA1
COPB2
COPG1
COPA
ASPM
SPTLC2
NCCRP1
SEMG2
CST4
SLC25A10
FTH1
SEMG1
FTL
NKAP
PPP1R13B
CCDC85C
AKAP9
DBNL
EME1
USP16
APBB1
KIF20A
NCOA4
HERC2
NEURL4
GCN1
SSSCA1
SPECC1L
CCDC186
CAPN1
ZNF106
NIN
CENPE
ZBTB5
MUS81
SORT1
DNAJC7
USP19
GTF3C2
KTN1
AIMP1
CEP170
SYNE2
BLMH
MAPK6
POLR2K
POLR2M
POLR2B
POLR2D
POLR2A
RPAP2
RPS27L
LARS
AIMP2
SAMM50
PATZ1
SNAPIN
MAP7D1
FNDC3A
TUBB6
POLR2I
POLR2C
KRT36
WDR62
KRT75
MAPKAPK5
TUBA1C
AUP1
POLR2H
POLR2J
POLR2G
KLC1
KIF5C
TTC37
KRT33B
PCM1
XPOT
SKIV2L
CEP55
NEK9
ATXN10
USMG5
KIF5B
SSX2IP
WWOX
ATAD3A
TUBB4A
KRT6B
CHCHD3
CEP104
CCDC6
VCP
TUBB3
TOMM22
IMMT
CBWD1
RAB2A
TUBB1
VDAC2
CBWD2
EIF3F
ATP6V1A
EIF3E
EIF3B
EIF3A
SLC25A12
EIF3G
PRRC2B
KLHL15
EIF3D
EIF3C
RER1
EIF3L
EIF3H
VPS4B
EIF3M
EIF3K
EIF3I
PELP1
EIF4G1
TEX10
USP9X
ARID1A
ARID1B
DPF3
PEG10
HLA-A
ERCC3
GTF2H4
RALGAPB
ATXN2
CTNNB1
TRPM7
SMARCD1
SMARCD2
SMARCA2
HLA-C
GTF2H1
GFOD1
LCP1
CTNNA1
C1QBP
CEP290
ACTBL2
CCP110
HLA-E
RALGAPA1
NEK11
APOBEC3F
COPS8
CEP97
HLA-H
FKBP5
ELAVL2
COPS3
KIRREL
WDR6
KIAA1217
UBE2O
TCHP
KRT79
PIKFYVE
SNX6
LTN1
SLK
SEC24A
SLC25A18
HEATR1
RGPD5
ESPL1
TMED10
SEC16A
MYO5A
NME7
KRT19
VAC14
SNX2
PTPN1
MAP4
TFG
SLC25A22
SLC27A2
RANGAP1
○ Prey in T-REx 293 and SH-SY5Y
□ Prey in T-REx 293 only
△ Prey in SH-SY5Y only
● ECH1 prey only
● ECI2 prey only
● HERC2 prey only
● NEURL4 prey only
● Prey of 2 baits
● Prey of 3 baits
● Prey of ≥ 4 baits
○ UBE3A prey
Edge with binary evidence
Edge with only non-binary evidence



A

Significance of closeness of CAMK2D preys to HUN core complex

B

Significance of closeness of HUN complex preys to CAMK2D preys

C

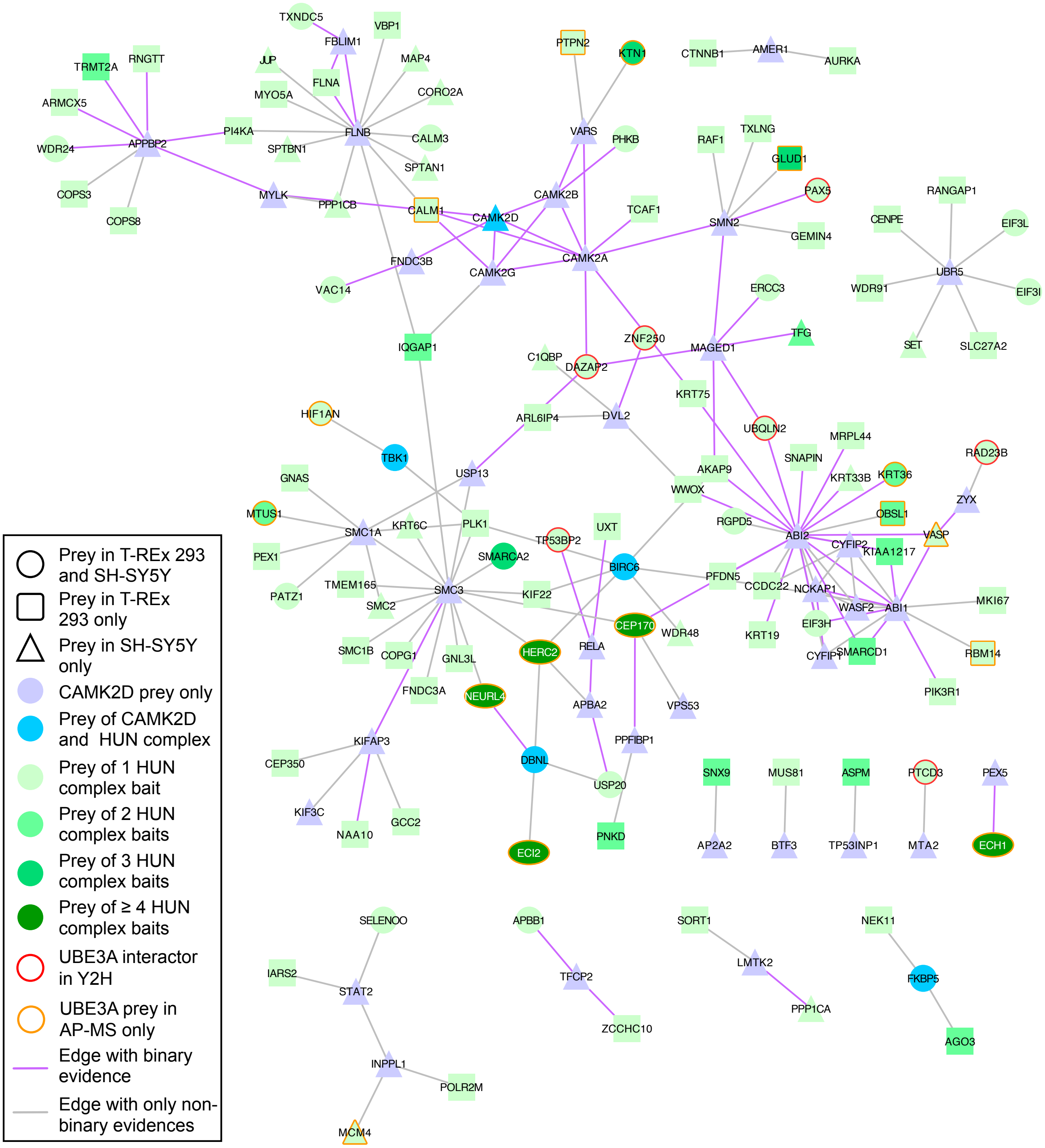
Significance of closeness of CAMK2D preys to UBE3A preys

D

Significance of closeness of HN complex preys to CAMK2D preys

Figure S5. The interaction networks of CAMK2D and the HUN complex are connected. Significances were empirically determined using 1000 degree-controlled randomized QBCHL networks. Red arrows indicate the real observation. The distribution of observations from the randomizations are displayed as grey histograms.

Figure S6.


TXNDC5
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FBLIM1
TRMT2A
RNGTT
JUP
MAP4
FLNA
MYO5A
CORO2A
ARMCX5
PI4KA
FLNB
CALM3
WDR24
APPBP2
SPTBN1
SPTAN1
COPS3
MYLK
PPP1CB
CALM1
COPS8
PTPN2
KTN1
CTNNB1
AMER1
AURKA
VARS
PHKB
RAF1
TXLNG
GLUD1
PAX5
CAMK2B
CAMK2D
TCAF1
SMN2
GEMIN4
RANGAP1
CENPE
EIF3L
FNDC3B
CAMK2A
CAMK2G
VAC14
ERCC3
WDR91
UBR5
EIF3I
IQGAP1
ZNF250
TFG
C1QBP
DAZAP2
MAGED1
SET
SLC27A2
HIF1AN
ARL6IP4
DVL2
KRT75
UBQLN2
MRPL44
TBK1
USP13
SNAPIN
RAD23B
GNAS
AKAP9
KRT33B
KRT36
WWOX
ZYX
MTUS1
KRT6C
PLK1
UXT
RGPD5
OBSL1
SMC1A
TP53BP2
ABI2
VASP
CYFIP2
PEX1
SMARCA2
KIAA1217
BIRC6
TMEM165
PFDN5
CCDC22
NCKAP1
PATZ1
SMC3
KIF22
SMC2
WASF2
ABI1
MKI67
CEP170
WDR48
KRT19
EIF3H
SMC1B
COPG1
GNL3L
HERC2
RELA
CYFIP1
SMARCD1
RBM14
FNDC3A
NEURL4
APBA2
VPS53
PIK3R1
KIFAP3
PPFIBP1
CEP350
DBNL
USP20
SNX9
MUS81
ASPM
PTCD3
PEX5
KIF3C
GCC2
NAA10
PNKD
ECI2
AP2A2
BTF3
TP53INP1
MTA2
ECH1
SELENOO
APBB1
SORT1
NEK11
IARS2
LMTK2
STAT2
TFCP2
FKBP5
PPP1CA
ZCCHC10
AGO3
INPPL1
POLR2M
MCM4
○ Prey in T-REx 293 and SH-SY5Y
□ Prey in T-REx 293 only
△ Prey in SH-SY5Y only
● CAMK2D prey only
● Prey of CAMK2D and HUN complex
● Prey of 1 HUN complex bait
● Prey of 2 HUN complex baits
● Prey of 3 HUN complex baits
● Prey of ≥ 4 HUN complex baits
○ UBE3A interactor in Y2H
○ UBE3A prey in AP-MS only
— Edge with binary evidence
— Edge with only non-binary evidences

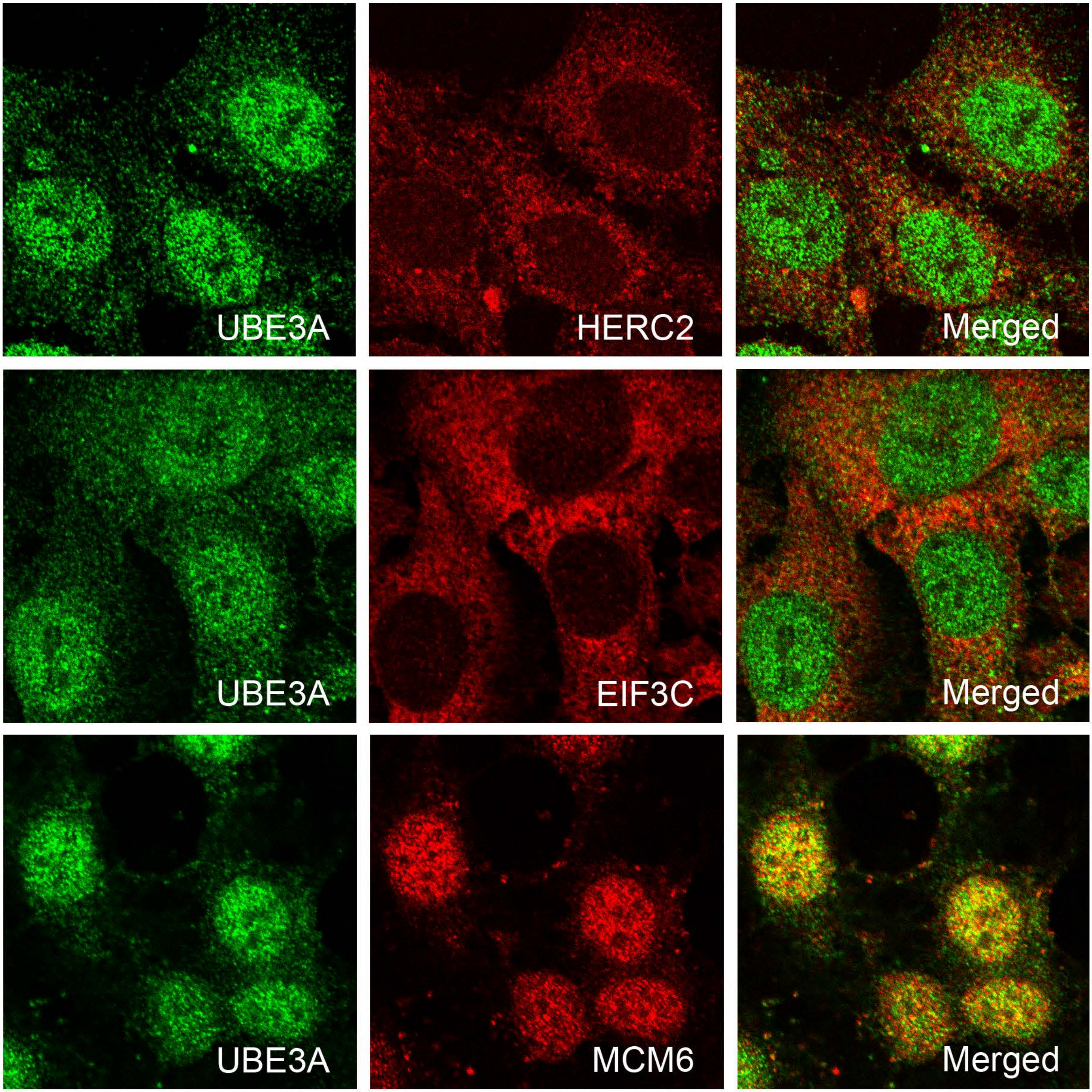

Figure S7. UBE3A partially colocalizes with HERC2, EIF3C, and MCM6 in HaCaT cells. UBE3A colocalizes with HERC2 and EIF3C in the cytosol and with MCM6 in the nuclei.

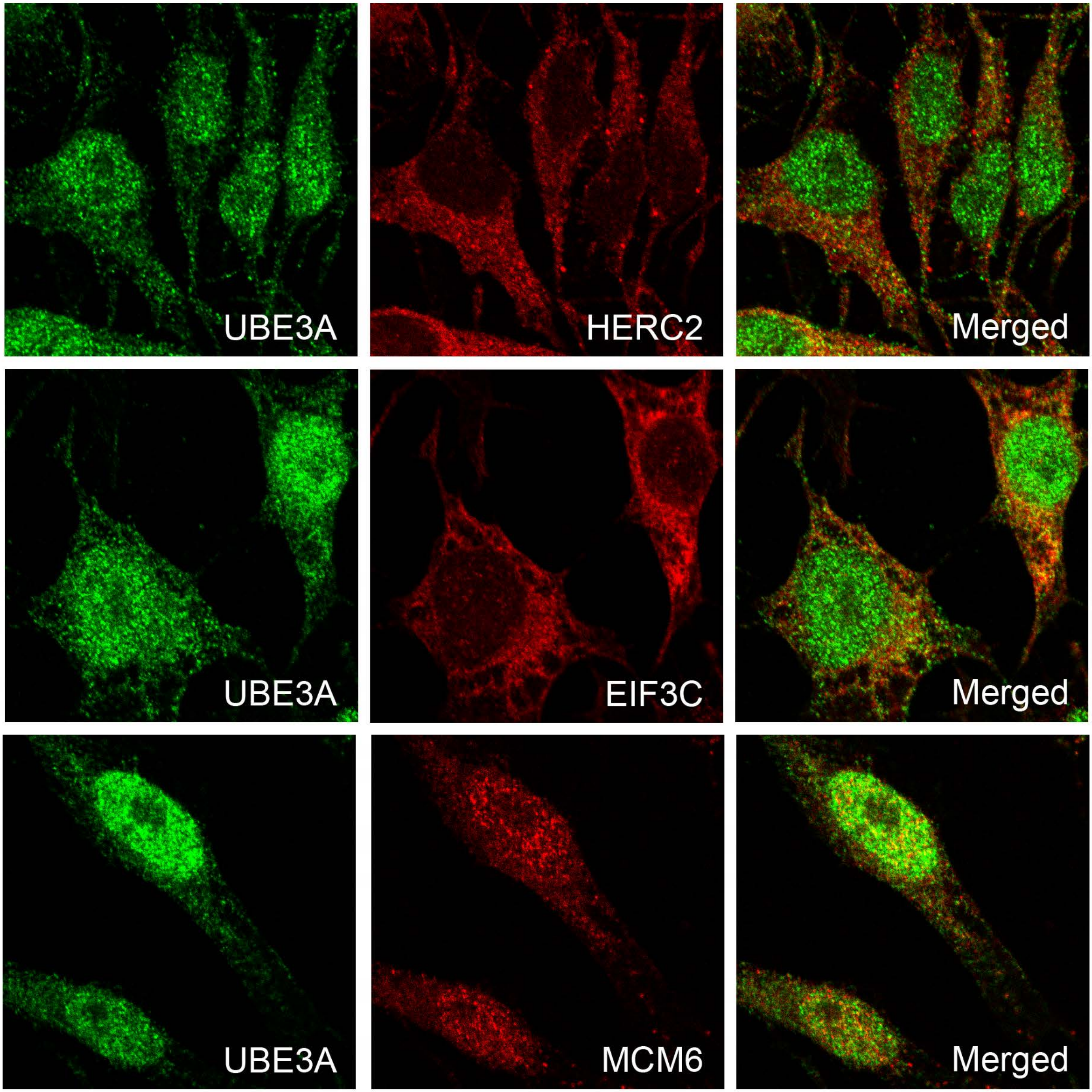

Figure S8. UBE3A partially colocalizes with HERC2, EIF3C, and MCM6 in HeLa cells. UBE3A colocalizes with HERC2 and EIF3C in the cytosol and with MCM6 in the nuclei.

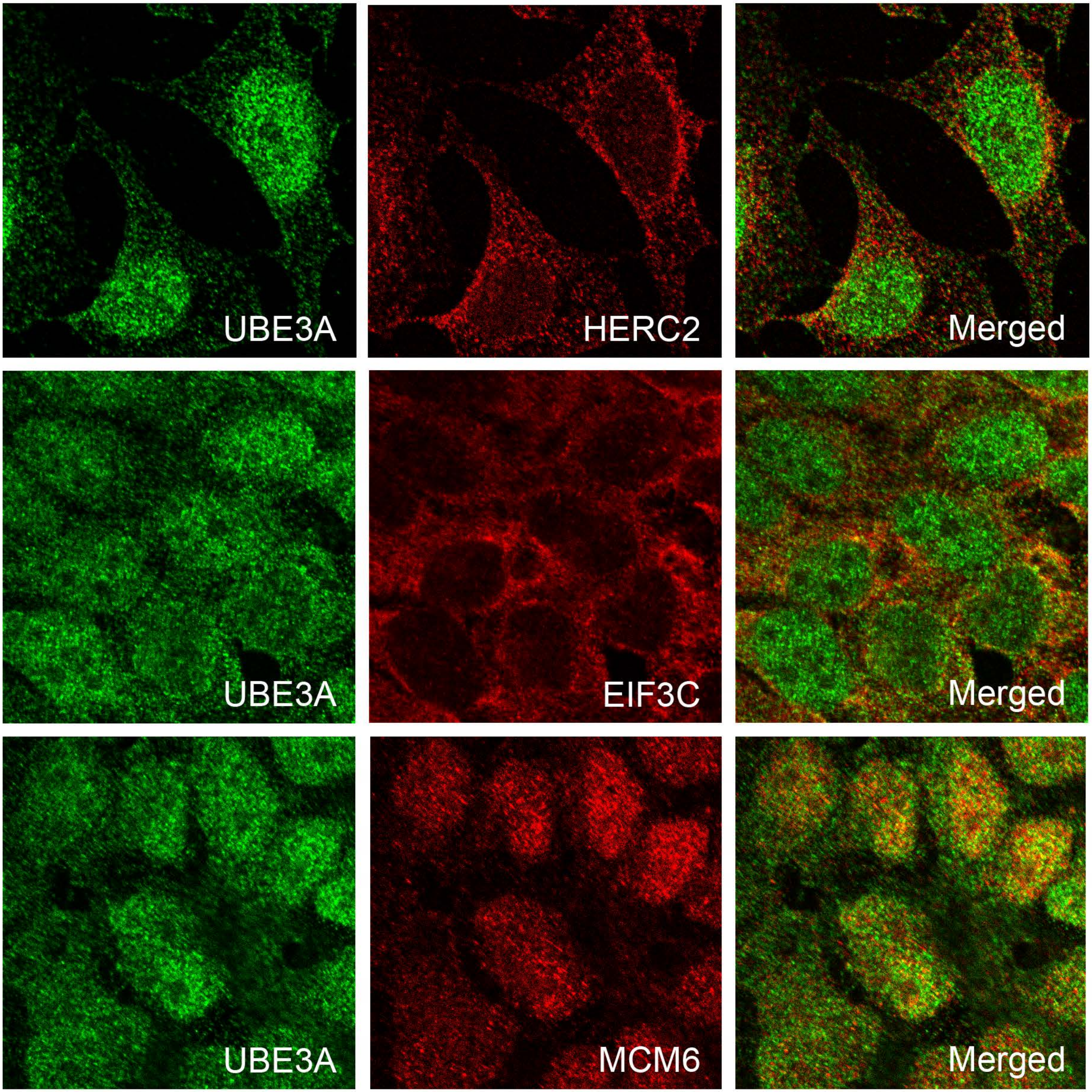

Figure S9. UBE3A partially colocalizes with HERC2, EIF3C, and MCM6 in U2OS cells. UBE3A colocalizes with HERC2 and EIF3C in the cytosol and with MCM6 in the nuclei.

Table S1. Summary of statistics to test the closeness of a given list of proteins in the QBCHL network.

seed_file	p_value	mean	std	z_score	num_nodes_real_network	size_real_LCC	num_equal_or_larger_rand_LCC	num_rand
CAMK2D_seed_file.txt	0.051	4.016	1.7256	2.30874	60	8	51	1000
ECH1_seed_file.txt	0.173	4.782	2.0896	1.06144	65	7	173	1000
ECI2_seed_file.txt	0	2.181	0.7989	6.03205	32	7	0	1000
HERC2_seed_file.txt	0	56.18	19.254	4.14566	278	136	0	1000
HIF1AN_seed_file.txt	0	3.424	1.3908	15.5138	50	25	0	1000
MAPK6_seed_file.txt	0	1.852	0.6404	9.60044	30	8	0	1000
NEURL4_seed_file.txt	0	8.666	4.0722	10.6415	134	52	0	1000
UBE3A_seed_file.txt	0.16	11.13	5.1922	1.12996	95	17	160	1000
UBE3A_seed_file_with_proteasome.txt	0	20.33	9.5641	5.61204	116	74	0	1000
UBE3A_seed_file_no_Y2H.txt	0.004	4.961	2.1775	4.1511	82	14	4	1000

P-values are determined based on comparison of the largest connected component (LCC) formed by the list of query proteins to the LCC formed by these query proteins in 1,000 degree-controlled random networks.

Table S2. Library of pulldowns from SH-SY5Y cells used as reference for CompPASS analysis.

[a] Bait	[b] Peptides	[c] Proteins
AKT1	341	351
AMPH	137	76
ARC	43	268
ARIH2	230	71
BEGAIN	121	222
BRCC3	35	151
BSND	95	692
CAMK2D	336	308
CDKL5	184	489
CHAF1B	83	540
CHEK2	127	316
CSK	441	208
ECH1	41	479
ECI2	24	353
FOSL1	10	408
GLTSCR1	75	527
GSK3B	54	87
HIF1AN	109	511
HPRT1	113	251
JUN	37	571
KIAA1217	195	590
MAML1	93	483
MAPK6	23	329
MECP2	99	561
MYC	9	542
NCOA4	18	522
NEDD4	239	136
NEURL4	111	566
NIPA1	9	271
ODC1	45	636
PARK2	141	181
PARK7	142	290
PHB	102	763
PLK1	108	578
PPP2CA	58	336
PRKCE	270	214
PTPN18	61	426
PXN	128	39
RBCK1	94	382
RCAN1	62	283
SNCA	84	489
SNCG	74	80
SPG21	64	211
SRC	207	80
STAT4	76	438
TCTE1	33	408
TGFB1I1	60	320
TIMP1	3	245
TP53	5	314
UBE3A	314	390
UBOX5	135	263
UBQLN2	105	297
UCHL3	177	48
UCHL5	135	206
USP14	537	250
USP15	365	237
USP16	31	289
USP20	64	311
USP5	598	194
VCPIP1	195	272
WFS1	441	403
WHSC1L1	167	684
WHSC2	128	473
WNK1	44	445

[a] Baits: HA-tagged protein used as bait in the HA-pulldown. [b] Peptides: total number of peptides of the bait protein detected by mass spectrometry. [c] Proteins: total number of proteins detected by mass spectrometry in a HA-pulldown.