

Table S1. Observed protein–protein interactions with E6AP

HECT E3 Ubiquitin Ligase (E.C.: 2.3.2.26)	Interacting protein	Detection Method	Region of interaction	References
E6-associated protein (E6AP, Ubiquitin-protein ligase E3A) Gene: UBE3A Chromosome location: 15q11.13 Ubiquitin Linkages: K48	14-3-3 protein gamma (14-3-3 γ , KCIP-1, YQHAG)	IF, PD		(Thatte and Banks, 2017)
	26S proteasome non-ATPase regulatory subunit 1 (PSMD1, RPN2)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 2 (PSMD2, TRAP2, RPN1)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 3 (PSMD3, RPN3)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 4 (PSMD4, RPN10, S5A)	2H, 3H, CE, IP, MS, PD, UbA, WB	AZUL (1-64aa)	(Kuhnle et al., 2018; Lee et al., 2014; Martinez-Noel et al., 2012; Martinez-Noel et al., 2018; Tomaic et al., 2013; Uchiki et al., 2009; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 5 (PSMD5, S5B)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 6 (PSMD6, PFAAP4, RPN7)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 7 (PSMD7, RPN8)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 8 (PSMD8, RPN12)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 10 (PSMD10, Gankyrin)	IP, MS		(Martinez-Noel et al., 2018)
	26S proteasome non-ATPase regulatory subunit 11 (PSMD11, RPN6)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 12 (PSMD12, RPN5)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 13 (PSMD13, RPN9)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome non-ATPase regulatory subunit 14 (PSMD14, RPN11)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome regulatory subunit 4 (PSMC1, P26s4, RPT2)	IP, MS		(Martinez-Noel et al., 2018)
	26S proteasome regulatory subunit 6A (PSMC3, TBP1, RPT5)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome regulatory subunit 6B (PSMC4, TBP7, MIP224)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome regulatory subunit 7 (PSMC2, LCMSS1, RPT1)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome regulatory subunit 8 (PSMC5, SUG1, TRIP1)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	26S proteasome regulatory subunit 10B (PSMC6, SUG2)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Activity-regulated cytoskeleton-associated protein (Arc, Arg3.1)	IP, PD, UbA		(Greer et al., 2010; Pastuzyn and Shepherd, 2017)
	Annexin A1 (ANXA1, ANX1, LPC1)	PD, UbA		(Shimoji et al., 2009)
	Apoptosis-stimulating of p53 protein 2 (TP53BP2, 53PB2, p53BP2, ASPP2, BBP)	2H, 3H, IP		(Martinez-Noel et al., 2018)
	B-lymphocyte kinase (Blk)	IP, PD, WB		(Oda et al., 1999)
	Bcl-2 homologous antagonist/killer (Bak)	IP, PD		(Thomas and Banks, 1998)
	Beta-actin-like protein 2 (ACTBL2)	IP, MS		(Martinez-Noel et al., 2018)
	Cellular tumor antigen p53 (p53, TP53)	2H, 3H, CE, CL, IF, IP, ITC, MS, PD, SPR, UbA, X-ray	280-781aa	(Alarcon et al., 1999; Ansari et al., 2012; Beaudenon et al., 2005; Cooper et al., 2003; Gewin and Galloway, 2001; Huibregtse et al., 1995; Huibregtse et al., 1991; Huibregtse et al., 1993a; Huibregtse et al., 1993b; Kao et al., 2000; Kuhnle et al., 2018; Martinez-Noel et al., 2018; Martinez-Zapien et al., 2016; Nakagawa and Huibregtse, 2000; Nuber et al., 1998; Ro et al., 2006; Sailer et al., 2018; Scheffner et al., 1994; Scheffner et al., 1993; Scheffner et al., 1995; Stutz et al., 2015; Talis et al., 1998; Thatte and Banks, 2017; White et al., 2012)
	Centrosomal protein of 170 kDa (CEP170, FAM68A, KAB, KIAA0470)	IP, MS		(Martinez-Noel et al., 2018)
	CGG triplet repeat-binding protein 1 (CGGBP1)	2H, 3H		(Martinez-Noel et al., 2018)
	Deleted in azoospermia-associated protein 2 (DAZAP2, KIAA0058)	2H, 3H		(Martinez-Noel et al., 2018)
	Delta(3,5)-delta(2,4)-dienoyl-CoA isomerase, mitochondrial (ECH1)	IP, MS		(Martinez-Noel et al., 2018)
	Dicks large (Dlg)	UbA, WB		(Kuballa et al., 2007)
	DNA replication licensing factor MCM6 (MCM6, p105MCM)	2H, 3H, MS, IF, IP		(Martinez-Noel et al., 2018)
	DNA replication licensing factor MCM7 (CDC47 homolog, P1.1-MCM3)	2H, IP, PD, UbA	L2G sequence (395-420aa)	(Kuhne and Banks, 1998)
	E6 protein (HPV16)	2H, 3H, Alpha,	LXXLL motif	(Be et al., 2001; Bedard et al., 2008; Beerheide et al.,

	CE, CL, DLS, ELISA, FBA, GPCA, IP, ITC, NMR, PD, SPR, TAP, UbA, WB, X-ray	(391-408aa)	1999; Beerheide et al., 2000; Bohl et al., 2000; Brimer et al., 2017; Brimer et al., 2007; Cherry et al., 2013; Cho et al., 2000; Chopjitt et al., 2015; Cooper et al., 2003; Daniels et al., 1997; Das et al., 2000; Elbel et al., 1997; Elston et al., 1998; Fei and de Villiers, 2008; Gewin and Galloway, 2001; Huibregtse et al., 1995; Huibregtse et al., 1991; Huibregtse et al., 1993a; Huibregtse et al., 1993b; Jeong et al., 2007; Jing et al., 2007; Kao et al., 2000; Karlsson et al., 2015; Kuballa et al., 2007; Lee et al., 2007; Liu et al., 2004; Malecka et al., 2014; Martinez-Noel et al., 2012; Martinez-Zapien et al., 2016; Nakagawa and Huibregtse, 2000; Nuber et al., 1998; Poirson et al., 2017; Rietz et al., 2016; Ro et al., 2006; Ronchi et al., 2014; Sailer et al., 2018; Scheffner et al., 1994; Scheffner et al., 1993; Scheffner et al., 1995; Sehr et al., 2007; Spangle et al., 2012; Srivenugopal and Ali-Osman, 2002; Stutz et al., 2015; Talis et al., 1998; Tan et al., 2012; Tomaic et al., 2013; Tomaic et al., 2011; Vos et al., 2009; Wang et al., 2010; White et al., 2012; Zanier et al., 2005; Zanier et al., 2013; Zanier et al., 2014; Zhou et al., 2011; Zimmermann et al., 1999)
Enoyl-CoA delta isomerase 2 (ECI2, DRS-1, HCA88, pECI)	IP, MS		(Martinez-Noel et al., 2018)
Estrogen receptor α (ESR1, ER α)	IP, PD		(Li et al., 2006)
Estrogen receptor β (ESR2, ER β)	IP, MS		(Kao et al., 2018)
Eukaryotic translation initiation factor 3 subunit C (eIF3c)	IF, IP, MS		(Martinez-Noel et al., 2018)
Golgi-associated PDZ and coiled-coil motif-containing protein (GOPC, PIST, CAL)	UbA, WB		(Jeong et al., 2007)
HECT domain and RCC1-like domain-containing protein 2 (HERC2)	2H, CE, IF, IP, MS, PD, Uba	150-200aa	(Galligan et al., 2015; Kuhnle et al., 2011; Kuhnle et al., 2018; Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
HECT-type E3 ubiquitin ligase UBR5 (UBR5, EDD, HYD, KIAA0896)	IP, PD		(Tomaic et al., 2011)
Hepatitis C virus E2 protein (HCV E2)	IP, WB		(Li et al., 2016)
Homeobox protein MOX-1 (MEOX1, MOX1)	2H, 3H		(Martinez-Noel et al., 2018)
Homeobox protein MOX-2 (MEOX2, MOX2, GAX)	2H, 3H		(Martinez-Noel et al., 2018)
Homeobox protein prophet of Pit-1 (PROP-1)	2H, 3H		(Martinez-Noel et al., 2018)
Hypoxia-inducible factor asparagine hydroylase (HIF1AN, HIF-1)	IP, MS		(Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
Immunoglobulin lambda constant 7 (IGLC7)	IP, MS		(Martinez-Noel et al., 2018)
Keratin, type II cytoskeletal 6B (KRT6B, K6B, KRTL1)	IP, MS		(Martinez-Noel et al., 2018)
Leukocyte C-terminal kinase (Lck)	PD		(Oda et al., 1999)
Lipocalin-1 (LCN1, Tlc, VEGP)	IP, MS		(Martinez-Noel et al., 2018)
MAP kinase-activated protein kinase 5 (MAPKAPK5, PRAK)	IP, MS		(Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
Melanoma-associated antigen 12 (MAGEA12, MAGE12)	2H, 3H		(Martinez-Noel et al., 2018)
Methyl-CpG binding protein 2 (MeCP2)	IP		(Kim et al., 2013)
Microtubule-associated protein 1B (LC1-MAP1B)	IP		(Grimaldo et al., 2017)
Mitogen-activated protein kinase 6 (MAPK6, ERK-3)	IP, MS		(Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
Na ⁺ /K ⁺ pump α subunit (ATP α)	UbA, WB		(Jensen et al., 2013)
NADH-ubiquinone oxidoreductase B16.6 subunit (GRIM-19; NDUFA13)	IP, PD	HECT	(Zhou et al., 2011)
Neuralized-like protein 4 (NEURL4, KIAA1787)	CE, IP, MS		(Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
Nuclear transcription factor X box-binding protein 1 (NFX1)	2H, IP		(Gewin et al., 2004)
O ⁶ -methylguanine-DNA methyltransferase (MGMT)	IP		(Srivenugopal and Ali-Osman, 2002)
Paired box protein Pax-5 (PAX5)	2H, 3H		(Martinez-Noel et al., 2018)
Paired box protein Pax-6 (PAX6)	2H, 3H		(Martinez-Noel et al., 2018)
Pentatricopeptide repeat domain-containing protein 3 (PTCD3, MRPS-39, TRG-15)	2H, 3H		(Martinez-Noel et al., 2018)
Peroxiredoxin 1	IP, PD, Uba		(Nasu et al., 2010)

	Progesterone receptor (PR, PGR, NR3C3)	2H, PD	170-449aa & 680-851aa	(Nawaz et al., 1999)
	Prolactin-inducible protein (PIP, gp17, GCDFP15)	IP, MS		(Martinez-Noel et al., 2018)
	Promyelocytic leukemia protein (PML, MYL TRIM19, RNF71)	IF, IP, UbA		(Louria-Hayon et al., 2009)
	Proteasome activator complex subunit 1 (PSME1, REG-alpha, IGUP I-5111, PA28a)	IP, MS		(White et al., 2012)
	Proteasome activator complex subunit 4 (PSME4, PA200, KIAA0077)	IP, MS		(White et al., 2012)
	Proteasome subunit alpha 1 (PSMA1, PSMA)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Proteasome subunit alpha type 2 (PSMA2, HC3, PSC3)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit alpha type-3 (PSMA3, HC8, PSC8)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Proteasome subunit alpha type-4 (PSMA4, HC9, PSC9)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit alpha type-5 (PSMA5)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit alpha type-6 (PSMA6, PROS-27, p27K)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit alpha type-7 (PSMA7, RC6-1, XAPC7)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit alpha beta type-9 (PSMB9, LMP2, PSMB6i, RING12)	IP, MS		(White et al., 2012)
	Proteasome subunit beta type-1 (PSMB1, PSC5)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Proteasome subunit beta type-2 (PSMB2)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit beta type-3 (PSMB3)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit beta type-4 (PSMB4, PROS-26)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit beta type-5 (PSMB5, LMPX, MB1)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit beta type-6 (PSMB6, LMPY)	IP, MS		(Martinez-Noel et al., 2018)
	Proteasome subunit beta type-7 (PSMB7, Macropain chain Z)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Proteasome subunit beta type-8 (PSMB8, LMP7, PSMC5i, RING10, Y2)	IP, MS		(Martinez-Noel et al., 2018; White et al., 2012)
	Protein kinase A (PKA)	Phos		(Thatte and Banks, 2017)
	Rabphilin-3A (RPH3A, Exophilin-1, KIAA0985)	3H		(Martinez-Noel et al., 2018)
	RING-type E3 ubiquitin transferase MID2 (MID2, FXY2, RFN60, TRIM1)	3H		(Martinez-Noel et al., 2018)
	RING1 and YY1-binding protein (RYBP, DEDAF, YEAF1)	IP, PD, UbA, WB		(Li et al., 2018)
	Ring1B (RF5)	CE, IP, MS, PD, UbA		(Li et al., 2018; Thatte and Banks, 2017; Zaoroor-Regev et al., 2010)
	S-methyl-5'-thioadenosine phosphorylase (MTAP)	IP, MS		(Martinez-Noel et al., 2018)
	Sacsin (DNAJC29)	IP		(Greer et al., 2010)
	Scribble (hScrib, LAP4, Vartul, KIAA0147)	IP, PD, UbA		(Nakagawa and Huibregts, 2000; White et al., 2012)
	Suppressor of G2 allele of SKP1 homolog (SUGT1, Sgt1)	IP, MS		(Martinez-Noel et al., 2018)
	Testis-specific basic protein Y 2 (BPY2, YCY2)	2H, IP	HECT domain	(Wong et al., 2002)
	Tetratricopeptide repeat 23-like (TTC23L)	2H, 3H		(Martinez-Noel et al., 2018)
	Transmembrane and coiled-coil domain-containing protein 7 (TMCO7, TANGO6)	IP, MS		(Martinez-Noel et al., 2018)
	Trihydrophobin 1 (TH1)	2H, IP, PD, UbA	N-terminus (1-280aa)	(Yang et al., 2007)
	Tuberous sclerosis 2 protein (Tuberin, TSC2)	IP, PD	260-316aa & 428-500aa	(Zheng et al., 2008)
	Tubulin beta-2B chain (TUBB2B)	IP, MS		(Martinez-Noel et al., 2018)
	Tyrosine-protein phosphatase non-receptor type 3 (PTPN3, PTP-H1)	TAP, UbA		(Jing et al., 2007)
	Ubiquilin-1 (UBQLN1, hPLIC-1)	2H, 3H, IP		(Kleijnen et al., 2000; Martinez-Noel et al., 2018)
	Ubiquilin-2 (UBQLN2, hPLIC-2)	2H, 3H, IP		(Kleijnen et al., 2000; Martinez-Noel et al., 2018)
	Ubiquitin carboxyl-terminal hydrolase 14 (USP14, TGT)	IP, MS		(Martinez-Noel et al., 2018)
	Ubiquitin carboxyl-terminal hydrolase isozyme L5 (UCHL5)	IP, MS		(Martinez-Noel et al., 2018)
	Ubiquitin-associated domain-containing protein 2 (UBAC2, PHGDHL1)	3H		(Martinez-Noel et al., 2018)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5)	Native-PAGE, PD, UbA	HECT	(Anan et al., 1998; Beaudenon et al., 2005; Hatakeyama et al., 1997; Kao et al., 2000; Nuber and Scheffner, 1999; Nuber et al., 1996; Sailer et al., 2018; Scheffner et al., 1994; Schwarz et al., 1998; Uchiki et al., 2009)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	2H, FP, IP, UbA, X-ray	HECT	(Anan et al., 1998; Grimaldo et al., 2017; Huang et al., 1999; Jeong et al., 2007; Kumar et al., 1997; Nuber et al., 1996; Nuber et al., 1998; Ronchi et al., 2017; Ronchi et

Ubiquitin-conjugating enzyme E2 L6 (UBE2L6, UBCH8, RIG-B)	2H, UbA	HECT	al., 2014; Ronchi et al., 2013; Sammond et al., 2007; Sammond et al., 2010; Schwarz et al., 1998; Yang et al., 2007; Zaoroor-Regev et al., 2010)	
Ubiquitin-conjugating enzyme E2 I1 (UBE2I, UBC9)	UbA		(Kumar et al., 1997; Scheffner et al., 1994; Scheffner et al., 1995)	
UV excision repair protein RAD23 homolog A (RAD23A, HHR23A)	2H, 3H, IP, PD, UbA		(Heaton et al., 2011)	
UV excision repair protein RAD23 homolog B (RAD23B, HHR23B)	2H, 3H, MS		(Greer et al., 2010; Kumar et al., 1997; Kumar et al., 1999; Martinez-Noel et al., 2018)	
Vasodilator-stimulated phosphoprotein (VASP)	IP, MS		(Martinez-Noel et al., 2018)	
Voltage-gated N-type calcium channel (Ca _{2.2} α ₁ subunit)	IP		(Martinez-Noel et al., 2018)	
Zinc finger protein 250 (ZNF250, ZNF647)	2H, 3H		(Grimaldo et al., 2017)	
Zinc finger protein 446 (ZNF446, ZKSCAN20)	2H, 3H		(Martinez-Noel et al., 2018)	

Detection methods: **2H**, yeast or mammalian-two hybrid; **3H**, yeast or mammalian-three hybrid; **Alpha**, amplified luminescent proximity homogenous assay; **CE**, co-elution during chromatography purification; **CL**, chemical crosslinking; **DLS**, dynamic light scattering; **ELISA**, enzyme-linked immunosorbent assay; **FBA**, *in vitro* filter binding assay; **FP**, fluorescence polarization; **GPCA**, *Gaussia* protein complementation assay; **IF**, immunofluorescence; **IP**, immunoprecipitation; **ITC**, isothermal calorimetry; **MS**, liquid chromatography or MALDI MS/MS; **Native-PAGE**, non-denaturing polyacrylamide gel electrophoresis; **NMR**, nuclear magnetic resonance; **PD**, pulldown using GST, His or MBP tag; **Phos**, *in vitro* phosphorylation; **SPR**, surface plasmon resonance; **TAP**, tandem affinity purification; **UbA**, ubiquitylation assay; **WB**, immunoblot; **X-ray**, X-ray crystallography.

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Table S2. Observed protein–protein interactions with NEDD4 family HECT E3 ubiquitin ligases

HECT E3 Ubiquitin Ligase (E.C.: 2.3.2.26)	Interacting protein	Detection Method	Region of interaction	References
HECT, C2 and WW domain containing E3 ubiquitin protein ligase 1 (HECW1; NEDL1) Gene: <i>HECW1</i> Chromosome location: 7q14.1-p13 Ubiquitin Linkages: K63? (TBD)	Dishevelled-1 (Dvl1)	2H, IP, UbA	WW 1 & 2	(Miyazaki et al., 2004)
	Mutant superoxide dismutase-1 (SOD1; mutations A4V, G93A, H46R)	2H, IP, UbA	CW linker (302-828aa)	(Miyazaki et al., 2004)
	Cellular tumor antigen p53 (p53, TP53)	IP		(Li et al., 2008b)
	RING finger protein 43 (RNF43)	2H, IP		(Shinada et al., 2011)
	Thyroid transcription factor 1 (TTF1, Nkx-2.1)	IP, UbA		(Liu et al., 2019a)
	Translocon-associated protein subunit-δ (TRAP-δ, SSR-δ)	2H, IP	WW 1 & 2	(Miyazaki et al., 2004)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA		(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA		(Kristariyanto et al., 2015; Miyazaki et al., 2004)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Kristariyanto et al., 2015; Miyazaki et al., 2004)
HECT, C2 and WW domain containing E3 ubiquitin protein ligase 2 (HECW2; NEDL2) Gene: <i>HECW2</i> Chromosome location: 2q32.3 Ubiquitin Linkages: K63	Anaphase-promoting complex subunit 1 (ANAPC1, APC1)	IP, MS		(Lu et al., 2013)
	Anaphase-promoting complex subunit 2 (ANAPC2, APC2)	IP, MS		(Lu et al., 2013)
	Anaphase-promoting complex subunit 4 (ANAPC4, APC4)	IP, MS		(Lu et al., 2013)
	Anaphase-promoting complex subunit 5 (ANAPC5, APC5)	IP, MS		(Lu et al., 2013)
	Anaphase-promoting complex subunit 7 (ANAPC7, APC7)	IP, MS		(Lu et al., 2013)
	Angiomotin-like protein 1 (AMOTL1)	IP, UbA	WW 1 & 2	(Choi et al., 2016)
	Angiomotin-like protein 2 (AMOTL1)	IP		(Choi et al., 2016)
	Angiomotin protein 130 (AMOTL130)	IP		(Choi et al., 2016)
	Cell division cycle protein 16 homolog (CDC16, APC6)	IP, MS		(Lu et al., 2013)
	Cell division cycle protein 23 homolog (CDC23, APC8)	IP, MS		(Lu et al., 2013)
	Cell division cycle protein 27 homolog (CDC27, APC3)	IP, MS		(Lu et al., 2013)
	Cellular tumor antigen p73 (p73, TP73)	IP, PD, UbA	WW 1 & 2	(Miyazaki et al., 2003)
	Centromere protein F (CENPF, CENF)	IP, MS		(Lu et al., 2013)
	Centrosomal protein of 170 kDa (CEP170, KAB)	IP, MS		(Lu et al., 2013)
	Cyttoplasmic linker-associated protein 2 (CLAPS2)	IP, MS		(Lu et al., 2013)
	Fizzy/cell division cycle 20 related 1 (FZR1, CDH1)	IP, MS, PD, UbA	C2 & CW linker (182-806aa)	(Lu et al., 2013)
	Heterochromatin protein 1α (HP1α)	IP, PD, UbA	WW 2	(Krishnamoorthy et al., 2018a)
E3 ubiquitin-protein ligase Itchy homolog (ITCH , Atrophin-1 Interacting Protein 4, AIP4) Gene: <i>ITCH</i> Chromosome location: 20q11.22 Ub linkage types: K29, K48,	Heterochromatin protein 1β (HP1β)	IP, PD, UbA	WW 2	(Krishnamoorthy et al., 2018a)
	Lamin A/C (LMNA, LMN1)	IP, UbA		(Krishnamoorthy et al., 2018b)
	Lamin B1 (LMNB1, LMN2, LMNB)	IP, UbA		(Krishnamoorthy et al., 2018b)
	Nucleolar and spindle-associated protein 1 (NUSAP1)	IP, MS		(Lu et al., 2013)
	Polo-like kinase 1 (PLK1, STPK13)	IP, MS		(Lu et al., 2013)
	Proliferating cell nuclear antigen (PCNA)	IP, UbA	HECT PIP (1321-1328aa)	(Krishnamoorthy et al., 2018b)
	Protein regulator of cytokinesis 1 (PRC1, ASE1)	IP, MS		(Lu et al., 2013)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA		(Miyazaki et al., 2003)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Miyazaki et al., 2003)
	Angiomotin/p130 (AMOT130)	IF, IP, MS, PD	WW 1 & 2	(Adler et al., 2013; Wang et al., 2012a)
Apoptosis-stimulating of p53 protein 2 (ASPP2, TP53BP2)	Apoptosis-stimulating of p53 protein 2 (ASPP2, TP53BP2)	IF, IP, MS, PD, TAP	WW 1-4	(Gao et al., 2015; Gen et al., 2017)
	Arrestin-2 (ARRB2)	IP, PD	WW 1 & 2	(Bhandari et al., 2007)
	Arrestin-3 (ARRB3)	2H, IP, UbA	WW 1-4	(Shea et al., 2012)
	Arrestin-4 (ARRB4)	2H, IP	WW 1-4	(Shea et al., 2012)
	Arrestin domain-containing protein 1 (ARRDC1)	PD, UbA		(Puca et al., 2013; Rauch and Martin-Serrano, 2011)
	Atrophin-1 (ATN1)	2H, PD		(Wood et al., 1998)

K63	β -p21-activated kinase-interactive exchange factor (β PIX)	IP, ITC, PD, X-ray	217-223aa	(Janz et al., 2007)
	BH3-interacting domain death agonist (Bid)	IP, UbA		(Azakir et al., 2010)
	CASP8 and FADD-like apoptosis regulator (CLFAR, c-FLIP _L)	IP		(Chang et al., 2006; Demange et al., 2009)
	Cleavage and polyadenylation specific factor 6 p68 subunit (CPSF6, CFlm)	IP, MS, PD	WW 1-4	(Ingham et al., 2005)
	Cleavage and polyadenylation specific factor 6 p25 subunit (CPSF6, CFlm)	IP, MS, PD	WW 1-4	(Ingham et al., 2005)
	Cylindromatosis (CYLD)	IP		(Zhang et al., 2013a)
	C-X-C chemokine receptor type 4 (CXCR4)	FRET, IP, PD, UbA	WW 1-4	(Bhandari et al., 2009; Bhandari et al., 2007; Malik et al., 2012; Marchese et al., 2003)
	Deltex-1 (DTX1)	IF, IP		(Chastagner et al., 2006)
	Dishevelled (Dvl)	2H, IP, UbA		(Wei et al., 2012)
	DNA-directed RNA Polymerase II largest subunit (RNA Pol II LS)	IP, MS, PD	WW 1-4	(Ingham et al., 2005)
	Dual specificity mitogen-activated protein kinase kinase 1 (MAP2K1, MKK1, MEK1)	2H, IP, PD, UbA		(Enzler et al., 2009)
	Dual specificity mitogen-activated protein kinase kinase 4 (MAP2K4, MKK4, MEK4)	FBA, IP, UbA		(Ahn and Kurie, 2009)
	Endophilin A1	IF, IP, PD, UbA	PRD	(Angers et al., 2004)
	E3 ubiquitin protein ligase CBL-C (CBLC, CBL3)	2H, IF, IP, PD	WW 1-4	(Courbard et al., 2002)
	E3 ubiquitin protein ligase DTX3L (Deltex-3-like, Rhysin-2)	IF, IP, PD, UbA		(Holleman and Marchese, 2014)
	Forkhead box protein O1 (FOXO1)	IP, UbA		(Xiao et al., 2014)
	Homeobox protein TGIF1 (TGIF)	IP	WW 1 & 2	(Demange et al., 2009)
	Human cytomegalovirus protein UL42 (HCMV UL42)	IF, IP	WW 1-4	(Koshizuka et al., 2016)
	Human enhancer of filamentation 1 (HEF1)	2H, IP, PD, UbA	WW 2-4	(Feng et al., 2004)
	Influenza A virus matrix protein (M1)	IF, IP		(Maheusithan et al., 2018; Su et al., 2013)
	Intersectin1 (ITSN1)	IP		(Dergai et al., 2018)
	Large tumor suppressor 1 (LATS1)	IP, MS, PD, UbA	WW 1-4	(Ho et al., 2011; Salah et al., 2011)
	Latent membrane protein 2A (LMP2A)	MS, IP	WW 1-4	(Winberg et al., 2000)
	Low-density-lipoprotein receptor class A domain containing 3 (LRAD3)	IP, PD	WW 1-4	(Noyes et al., 2016)
	Low-density-lipoprotein receptor-related protein 6 (LRP6)	MS, IP, UbA		(Vijayakumar et al., 2017)
	Matrix protein VP40 (eVP40)	IP, PD	WW 1	(Han et al., 2016)
	MicroRNA 106b (has-miR-106b)	IP		(Luo et al., 2016)
	Mitochondrial antiviral-signaling proteins (MAVS)	IP, UbA	WW 2 & 3	(You et al., 2009)
	Mitogen-activated protein kinase 8 (MAPK8, JNK1)	IP, UbA	595-604aa	(Gallagher et al., 2006)
	Mitogen-activated protein kinase kinase kinase 7 (MAP3K7, Tak1)	IP		(Ahmed et al., 2011)
	NEDD4-binding partner-1 (N4BP1)	IP, PD	WW 2	(Oberst et al., 2007)
	NEDD4 family-interacting protein 1 (NDFIP1)	IP, UbA		(Jiang et al., 2019; Kathania et al., 2015)
	Neurogenic locus notch homolog protein 1 (Notch)	IP, PD, UbA	WW 1-4	(McGill and McGlade, 2003; Puca et al., 2013; Qiu et al., 2000)
	Nuclear factor of activated T-cells, cytoplasmic 1 (NFATc)	IP		(Fang et al., 2002)
	Ocludin (OCLN)	2H, IP, UbA	WW 2 & 4	(Traweger et al., 2002)
	Octamer-binding transcription factor 4 (Oct4, POU5F1)	IP, MS, PD, TAP		(Liao et al., 2013)
	Patched-1 (PTCH1)	IF, IP, MS		(Chen et al., 2014)
	Phosphatidylinositol 4-kinase II α (PI4KII α)	IF, IP, NMR, PD, UbA	WW 3	(Mossinger et al., 2012)
	Phospholipase C-gamma-1 (PLC- γ 1)	IP		(Heissmeyer et al., 2004)
	Protein numb homolog (Numb)	IP, PD	WW 1 & 2	(Di Marcotullio et al., 2011; McGill and McGlade, 2003)
	Ras association domain-containing protein 5 (RASSF5, NORE1)	IP, PD, UbA	WW 1-4	(Suryaraja et al., 2013)
	Receptor-interacting serine/threonine-protein kinase 1 (RIPK1, RIP1)	IP, UbA		(Shembade et al., 2008)
	Receptor-interacting serine/threonine-protein kinase 2 (RIPK2, RIP2)	IP, PD		(Perez et al., 2018)
	Receptor tyrosine-protein kinase erbB-3 (ERBB3, HER3)	IF, IP, PD	WW 1-4	(Le Clorennec et al., 2016; Omerovic et al., 2007)
	Receptor tyrosine-protein kinase erbB-4 (ErbB4, HER4)	IP, MS		(Gilmore-Hebert et al., 2010)
	RNA-binding protein EWS (EWS)	IP, MS, PD	WW 2	(Ingham et al., 2005)
	RING finger protein 11 (RNF11, CGI-123)	IP, PD	WW 1	(Kitching et al., 2003; Shembade et al., 2009)
	Serine/threonine-protein kinase Sgk3 (SGK3, SGKL, CISK)	2H, IP, PD	WW 1-4	(Slagsvold et al., 2006)

	Signal transducing adapter molecule 1 (STAM-1)	IF, IP, PD	PRD	(Malik et al., 2012)
	SMAD family member 2 (SMAD2)	IP, UbA		(Bai et al., 2004)
	SMAD family member 7 (SMAD7)	2H, IP, UbA	WW 1 & 2	(Gen et al., 2017; Lallemand et al., 2005; Park et al., 2015)
	Sorting nexin 9 (SNX9)	IP, PD, MS, UbA	PRD	(Baumann et al., 2010)
	Sorting nexin 18 (SNX18)	IP		(Baumann et al., 2010)
	Spartin (SPG20)	IF, IP	PRR + WW 1-4	(Edwards et al., 2009; Hooper et al., 2010)
	Src homology region 2 domain-containing phosphatase-1 (SHP-1, PTPN6)	IP, MS, UbA		(Aki et al., 2018)
	Tax1-binding protein 1 (TAX1BP1, T6BP)	IP		(Shembade et al., 2008)
	TGF-beta-activated kinase 1 and MAP3K7-binding protein 1 (TAB1)	MS, IP, PD	WW 1-4	(Theivarthiran et al., 2015)
	TGF-beta inducible early growth response protein 1 (TIEG1)	IP, UbA	WW 1-4	(Venuprasad et al., 2008)
	Thioredoxin-interacting protein (TXNIP)	IF, IP	WW 1-4	(Otaki et al., 2016; Zhang et al., 2010a)
	TNF receptor-associated factor 6 (TRAF6)	DeUbA, IP		(Zhang et al., 2013a)
	Trans-acting T-cell-specific transcription factor GATA-3	IP		(Fang et al., 2002)
	Transcription factor AP-1 (c-Jun, Jun)	IF, IP		(Fang et al., 2002; Fang and Kerppola, 2004; Gao et al., 2004)
	Transcription factor Jun-B (JunB)	IP, PD, UbA	WW 1-4	(Fang et al., 2002; Liu et al., 2019c)
	Transcription factor Maf (c-Maf)	IP		(Fang et al., 2002)
	Transcription factor NF-E2 45 kDa subunit (p45 NF-E2)	2H, IF, PD, UbA	WW 1	(Chen et al., 2001; Lee et al., 2008a)
	Tumor protein p63 (p63)	IF, IP, NMR	WW 1 & 2	(Bellomaria et al., 2010; Bellomaria et al., 2012; Melino et al., 2014; Rossi et al., 2006a; Rossi et al., 2006b)
	Tumor protein p73 (p73)	IP, TAP, UbA		(Rossi et al., 2005)
	Tyrosine-protein kinase Fyn (Fyn)	IP, MS		(Yang et al., 2006)
	Ubiquitin-associated protein 2-like (UBAP2L, NICE4, KIAA0144)	IP, MS, PD	WW2	(Ingham et al., 2005)
	Ubiquitin carboxyl-terminal hydrolase CYLD (CylD)	IP, PD		(Ahmed et al., 2011)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Kristariyanto et al., 2015; Wang et al., 2019)
	Ubiquitin-conjugating enzyme E3 D2 (UBE2D2, UBCH5B)	UbA		(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E3 D3 (UBE2D3, UBCH5C)	UbA		(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E2 E1 (UBE2E1, UBCH6)	UbA		(Ahn and Kurie, 2009)
	Ubiquitin-conjugating enzyme E2 G1 (UBE2G1, UBC7)	UbA		(Gallagher et al., 2006)
	Ubiquitin-conjugating enzyme E3 L3 (UBE2L3, UBCH7, UBCE7)	IP, PD, SPR, UbA		(Kristariyanto et al., 2015; Perez et al., 2018; Puca et al., 2013)
	WW domain containing E3 ubiquitin protein ligase 2 (WWP2)	IP, MS	WW 3	(Aki et al., 2018)
	Zinc finger protein GLI1 (GLI1)	IP, PD, UbA	WW 1, 2, & 4	(Di Marcotullio et al., 2011; Wang et al., 2017c)
Neural precursor cell expressed developmentally down-regulated 4, E3 ubiquitin ligase; (NEDD4; NECD4-1; Cell proliferation-inducing gene 53 protein; HECT-type E3 ubiquitin transferase NECD4; RPF1) Gene: NEDD4 Chromosome location: 15q21.3 Ubiquitin Linkages: K6, K27, K48, K63	α -synuclein (α S, NACP)	IF, IP, MS, UbA		(Kim et al., 2016b; Sugeno et al., 2014; Tofaris et al., 2011)
	α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA receptor, quisqualate receptor)	IP, UbA		(Lin et al., 2011; Rodrigues et al., 2016)
	Activated Cdc42-associated tyrosine kinase (ACK)	IP, PD, UbA	WW 3	(Lin et al., 2010)
	Activation-induced cytidine deaminase (AICDA, AID)	IP, UbA		(Sun et al., 2013)
	ADP-ribosylation factor-binding protein GGA3 (GGA3, KIAA0154)	IP, UbA		(Pak et al., 2006)
	Angiomotin-like 1 (AMOTL1)	IP		(Ray et al., 2019)
	Annexin XIIIb	IF, IP, MS, PD	C2	(Plant et al., 2000)
	Arrestin domain containing protein 3 (ARRDC1)	2H	WW	(Rauch and Martin-Serrano, 2011)
	Arrestin domain containing protein 3 (ARRDC2)	2H	WW	(Rauch and Martin-Serrano, 2011)
	Arrestin domain containing protein 3 (ARRDC3)	2H, IF, IP, ITC, X-ray	WW 1-4	(Nabhan et al., 2010; Qi et al., 2014; Rauch and Martin-Serrano, 2011)
	Arrestin domain containing protein 3 (ARRDC4)	2H	WW	(Rauch and Martin-Serrano, 2011)
	ATP-binding cassette transporter 1 (ABCG1, ABC8, WHT1)	IP, MS		(Aleidi et al., 2015)
	ATP-binding cassette transporter 4 (ABCG4, WHITE2)	IP, MS		(Aleidi et al., 2015)
	Aquaporin-2 (AQP2)	2H, IP, UbA	WW 1-4	(Trimpert et al., 2017)
	β -arrestin-1	IF, IP		(Simonin and Fuster, 2010)
	β -arrestin-2	2H	WW	(Rauch and Martin-Serrano, 2011)

β_2 -adrenergic receptor (β_2 AR, ADR β_2 R)	IP, UbA		(Nabhan et al., 2010; Shenoy et al., 2008)
Bean1	FW, PD	WW 2 & 3	(Jolliffe et al., 2000)
Beclin-1 (BECN1)	2H, IP, PD, UbA	WW 1-4	(Pei et al., 2017; Platta et al., 2012)
Calpain 2 (CAPN2)	IP, PD, UbA		(Cui et al., 2014)
Caspase 11 (Casp11)	IP, MS, UbA		(Liu et al., 2019b)
Cezanne-1 (OTUD7B)	IP	WW	(Pareja et al., 2012)
Commissureless (Comm)	2H, IF, IP, PD	WW 2 & 3	(Myat et al., 2002)
Connexin43 (Cx43)	IF, IP, ITC, NMR, PD, SPR	WW 1-3	(Leykauf et al., 2006; Spagnol et al., 2016)
Cyclic nucleotide ras guanine-exchange factor (CNrasGEF)	IP, PD, UbA	WW 1-4	(Pham and Rotin, 2001)
Deoxycytidine deaminase (APOBEC3G, CEM15)	IP, PD, UbA	WW 2 & 3	(Dussart et al., 2005)
Discs large homolog 3 (Dlg3)	IF, IP, MS, TAP, UbA		(Van Campenhout et al., 2011)
DNA damage-inducible transcript 4 protein (DDIT4, RTP801)	IF, IP, UbA		(Canal et al., 2016)
E3 ubiquitin ligase Cbl-b (Cbl-b, RNF56)	IP, UbA		(Yang et al., 2008)
Ebola Viral matrix protein (VP40)	IP, ITC, NMR, UbA	WW 1-4	(Iglesias-Bexiga et al., 2019; Malakhova and Zhang, 2008; Okumura et al., 2008; Yasuda et al., 2003)
Epithelial Na ⁺ channel (ENaC)	2H, FP, IP, NMR, PD, SPR	WW 2, 3 & 4	(Bobby et al., 2013; Farr et al., 2000; Goulet et al., 1998; Harvey et al., 1999; Henry et al., 2003; Kamynina et al., 2001b; Kanelis et al., 2000; Kanelis et al., 1998; Kanelis et al., 2001; Lott et al., 2002; Snyder et al., 2001; Staub et al., 1996)
Exportin-1 (Exp1, XPO1)	IP, UbA		(Xu et al., 2019)
Fibroblast growth factor receptor 1 (FGFR1, FLT-2)	FP, IP, PD, UbA	C2 & WW 3	(Persaud et al., 2011)
$\gamma 2$ -adaptin	IP, PD		(Rost et al., 2006)
G-protein-coupled receptor 183 (GPR183)	IP		(Zhang et al., 2015)
G-protein-coupled receptor kinase 2 (GRK2)	IP, Phos	WW 2 & 3	(Sanchez-Perez et al., 2007)
Growth factor receptor bound protein 10 (Grb10)	2H, CE, IP, PD, X-ray	C2	(Huang and Szelenyi, 2010; Monami et al., 2008; Morrione et al., 1999; Vecchione et al., 2003)
GTPase KRas (K-Ras)	IF, MS, PD, UbA		(Zeng et al., 2014)
Guanylyl cyclase domain containing 1 (GUCD1)	2H, IF, IP, UbA		(Bellet et al., 2014)
Heat shock transcription factor 1 (HSF1)	IP, UbA		(Kim et al., 2016b)
Herpes simplex virus UL 56 protein (HSV UL56)	2H, IF, IP	WW 1-4	(Ushijima et al., 2008)
Histone H3	IP, PD, UbA		(Zhang et al., 2017a)
Hormonally up-regulated neu tumor-associated kinase (HUNK, MAK-V)	2H, IP, MS, PD	C2 and WW 1	(Kalinichenko et al., 2012)
Human epidermal growth factor receptor 3 (HER3)	IF, IP, MS, UbA	WW 1-4	(Huang et al., 2015)
Human immunodeficiency virus type 1 (HIV-1) Gag protein	IP	C2 & WW 1-4	(Sette et al., 2010)
Human proline-rich transcript, brain-expressed protein (hPRTB)	2H, IF, PD, UbA	WW 1-4	(Hamilton et al., 2001)
Human T-cell leukemia virus type 1 Gag (HTLV1-Gag)	2H, IF, ITC, NMR, PD	WW 1-4	(Bouamri et al., 2003; Iglesias-Bexiga et al., 2019; Sakurai et al., 2004)
Insulin-like growth factor receptor (IGF-1R β)	IF, IP, UbA		(Kwak et al., 2012; Monami et al., 2008; Vecchione et al., 2003)
Insulin receptor substrate 2 (IRS-2)	IP, MS, PD, UbA	C2	(Fukushima et al., 2017; Fukushima et al., 2015)
Interferon-induced gene 15 (ISG15)	IP, UbA		(Hu et al., 2019; Malakhova and Zhang, 2008; Okumura et al., 2008)
Interferon-induced transmembrane protein 3 (IFITM3)	IF, IP, UbA	WW 1-4	(Chesarino et al., 2015)
Large tumor suppressor kinase 1 (LATS1, WARTS protein kinase)	IF, IP, PD, PepA, UbA	WW 1-4	(Bae et al., 2015; Salah et al., 2013)
Low-density-lipoprotein receptor class A domain containing 3 (LRAD3)	IP, MS, PD, UbA	WW	(Noyes et al., 2016)
Lysosomal protein transmembrane 4 (LAPTM4)	IF, IP, UbA	WW 1-4	(Milkereit and Rotin, 2011)
Lysosomal protein transmembrane 5 (LAPTM5)	IP, UbA	WW 2	(Fouladkou et al., 2008; Pak et al., 2006)
Mahogunin ring finger-1 (MGRN1, RNF156)	IP		(Gunn et al., 2013)

Microtubule associated protein 1 light chain 3 (LC3)	IF, FP, IP, PD, UbA, X-ray	LIR (Between C2 & WW 2)	(Ogawa et al., 2018; Pei et al., 2017; Qiu et al., 2017; Sun et al., 2017)
Mitogen-activated protein kinase (MAPK) p38α	IP, MS, UbA	WW 1-4	(Liu et al., 2017)
Mouse double minute 2 homolog (MDM2)	MS, PD, UbA		(Xu et al., 2015)
Myotubularin-related protein 4 (MTMR4)	IF, IP, UbA	WW 1-4	(Plant et al., 2009)
Na ⁺ H ⁺ exchanger 1 (NHE1, APNH)	IF, IP, UbA		(Simonin and Fuster, 2010)
Nedd4-binding partner-1 (N4BP1)	2H, IP, PD, UbA	WW 1-4	(Murillas et al., 2002)
Nedd4-binding partner-2 (N4BP2)	2H, FW, IP, PD, UbA	WW 2	(Jolliffe et al., 2000; Murillas et al., 2002)
Nedd4-binding partner-3 (N4BP3, KIAA0341)	2H, FW, IF, PD, UbA	WW 1-3	(Jolliffe et al., 2000; Murillas et al., 2002)
Nedd4-binding partner-4 (N4BP4)	2H, FW, PD	WW 1-3	(Jolliffe et al., 2000; Murillas et al., 2002)
Nedd4-binding partner-5 (N4BP5)	FW, IP	WW 1-3	(Harvey et al., 2002; Jolliffe et al., 2000)
Nedd4-family interacting protein 1 (NDFIP1)	IF, IP, PD, UbA		(Jiang et al., 2019; Lackovic et al., 2012; Trimpert et al., 2017)
Nedd4-family interacting protein 1 (NDFIP2)	IP, UbA		(Trimpert et al., 2017)
Neurogenic locus notch homolog protein 1 (Notch 1, TAN1)	IP	WW 1-3	(Koncarevic et al., 2007; Sakata et al., 2004; Zhang et al., 2015)
NMDA receptor subunit GluN2D	2H, IP, MS, UbA	WW 2 & 3	(Gautam et al., 2013)
N-myc downstream regulated gene 1 protein (NDRG1, CAP43)	IP		(Verma et al., 2017)
Paired box protein Pax-7 (Pax7)	IF, PD, UbA		(Bustos et al., 2015)
PDZ and LIM domain protein 7 (PDLIM7, Enigma)	IF, IP, MS, PD, UbA	WW 2 & 3	(D'Cruz et al., 2016)
Peroxisome proliferator-activated receptor- γ (PPAR γ)	IP, UbA		(Li et al., 2016)
Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN (PTEN, MMAC1, TEP1)	IF, IP, MS, PD, UbA		(Drinjakovic et al., 2010; Fouladkou et al., 2008; Kwak et al., 2010; Wang et al., 2007)
Programmed cell death 6-interacting protein (PDVD6IP, Alix)	2H, IP, UbA		(Sette et al., 2010)
Protein kinase B (AKT)	IF, IP, UbA		(Fan et al., 2013)
Protein salvador homolog 1 (SAV1, WW45)	IP, PD, UbA	C2	(Bae et al., 2015)
Protein sprout homolog 2 (Spry2)	IF, IP, PD, UbA	WW 1-3	(Edwin et al., 2010)
Protein tyrosine kinase 2 (PYK2)	IP		(Verma et al., 2017)
Pulmonary surfactant-associated protein C (SP-C, SP5)	IP, PepA		(Kotorashvili et al., 2009)
Ras-related C3 botulinum toxin substrate 1 (Rac1, Ras-like protein TC25)	IF, IP, MS, PD	WW 1-4	(Nethe et al., 2012)
Ras-related protein Rap-2A (RAP2A)	IP, PD, UbA		(Kawabe et al., 2010; Wang et al., 2017a)
Rearranged during transfection receptor tyrosine kinase 9 (RET9)	IP, UbA		(Hyndman et al., 2017)
Receptor tyrosine-protein kinase erbB-4 (ErbB4, HER4)	IP, PD	WW 1-4	(Zeng et al., 2009)
RING box protein 2 (Rbx1, ROC1, RNF7, SAG)	IP, UbA	HECT	(Zhou et al., 2014)
RING finger protein 11 (RNF11)	PD, UbA	WW	(Santonico et al., 2010)
RING-type E3 ubiquitin ligase TRAF3 (TRAF3)	IP, MS, UbA	WW	(Fang et al., 2014)
RNA-binding protein NANOS2	IF, IP, PD, UbA		(Zhou et al., 2017b)
RNA polymerase II (RNAPII)	UbA		(Anindya et al., 2007)
Rous sarcoma virus L-domain of Gag (RSV Gag)	IP	WW 1-4	(Kikonyogo et al., 2001)
SCF ^β -TRCP ubiquitin E3 ligase complex	IP, PD, UbA		(Liu et al., 2014)
Segment polarity protein disheveled homolog-1 DVL-1 (Dvl1)	IP, PD, UbA	WW 1-4	(Nethe et al., 2012)
Serine/threonine-protein kinase ULK1 (ATG1)	IP		(Pei et al., 2017)
SERTA domain-containing protein 1 (p34 ^{SE-1})	IP, NMR, PD, UbA	WW 1	(Hong et al., 2014; Shrestha et al., 2017)
Serum/glucocorticoid-regulated kinase 1 (SGK1)	PD, SPR	WW 1 & 3	(Wiemuth et al., 2010)
Sequestosome-1 (SQSTM1, p62)	IP, PD, UbA		(Sun et al., 2017)
SMAD family member 1 (SMAD1)	IF, IP, UbA		(Kim et al., 2011)
Small integral membrane protein of lysosome/late endosome (SIMPLE, LITAF)	IF, IP		(Shirk et al., 2005)
Solute carrier family 22 member 6 (organic anion transporter 1, hOAT1)	IP, UbA		(Xu et al., 2016b)

	Speedy protein A (Spy1, RINGOA)	IP, UbA	WW 1-4	(Al Sorkhy et al., 2009)
	Thioredoxin-interacting protein (TXNIP)	2H	WW	(Rauch and Martin-Serrano, 2011)
	THO complex subunit 1 (Thoc1, p84)	IP, PD, UbA		(Song et al., 2013)
	Traf2- and Nck-interacting protein kinase (TNIK)	IP, PD		(Wang et al., 2017b)
	Transmembrane prostate androgen-induced protein (TMEPA1, STAG1)	IP, PD, UbA	WW 2 & 3	(Jing et al., 2015; Li et al., 2008a)
	Tumor protein 63 (p63, p73-like)	2H, IP, UbA		(Bakkers et al., 2005)
	Ubiquitin-conjugating enzyme E3 D1 (UBE2D1, UBCH5A)	UbA		(Wang et al., 2019)
	Ubiquitin-conjugating enzyme E3 D2 (UBE2D2, UBCH5B)	UbA		(Bustos et al., 2015; Fotia et al., 2006; Murillas et al., 2002; Sugeno et al., 2014)
	Ubiquitin-conjugating enzyme E3 D3 (UBE2D3, UBCH5C)	UbA	HECT	(Hong et al., 2014; Jiang et al., 2019; Maspero et al., 2011)
	Ubiquitin-conjugating enzyme E2 E1 (UBE2E1, UBCH6)	UbA		(Zhang et al., 2017a)
	Ubiquitin-conjugating enzyme E3 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Zhang et al., 2017a)
	WW domain-binding protein 1 (WBP-1)	FW	WW 2 & 3	(Jolliffe et al., 2000)
	WW domain-binding protein 2 (WBP-2)	FW	WW 2 & 3	(Jolliffe et al., 2000)
	Zinc finger protein GLI-similar 3 (GLIS3, ZNF515)	2H, IP, MS, UbA	WW 1-4	(ZeRuth et al., 2015)
	5'-AMP-activated protein kinase (AMPK)	IP, MS, Phos, UbA		(Bhalla et al., 2006; Ho et al., 2018)
	14-3-3 protein	IP		(Chandran et al., 2011; Ho et al., 2018; Lee et al., 2018; Zhu et al., 2017)
	Activated Cdc42 kinase 1 (ACK1)	IF, IP, MS, PD	WW 1-4	(Chan et al., 2009)
	Amyloid-beta A4 precursor protein-binding family B member 1 (APBB1, Fe65)	IF, IP, UbA	C2	(Lee et al., 2009)
	Angiomotin-like 1 (AMOTL1)	IF, IP, MS, UbA	WW 3	(Ray et al., 2019; Skouloudaki and Walz, 2012)
Neural precursor cell expressed developmentally down-regulated 4-like, E3 ubiquitin ligase (<u>NEDD4L</u> ; NEDD4-2; RSP5; PVNH7; NEDD4.2; Hnedd4-2) Gene: <u>NEDD4L</u> Chromosome location: 18q21.31 Ubiquitin Linkages: K6, K27, K29, K63	Aquaporin-2 (AQP2)	IP, UbA		(Trimpert et al., 2017)
	c-Abelson tyrosine kinase (c-Abl)	IP, MS		(Skouloudaki and Walz, 2012)
	cAMP-responsive element-binding (CREB)-regulated transcription coactivator 3 (CRTC3, TORC3)	IP, PD, UbA	WW 2	(Kim et al., 2018)
	cAMP-dependent protein kinase (PKA)	IP, , MS, Phos	WW 1-3	(Andersen et al., 2015; Snyder et al., 2004)
	Caveolin-3 (Cav3)	IF, IP		(Guo et al., 2012)
	Cystic fibrosis transmembrane conductance regulator (CFTR)	IP, UbA		(Caohuy et al., 2009)
	Discs large homolog 3 (Dig3, SAP102)	IF, IP, MS, TAP	WW 1-4	(Van Campenhout et al., 2011)
	Dishevelled 2 (Dvl2)	IF, IP, PD, UbA	WW 2 & 3	(Ding et al., 2013)
	Dopamine transporter (DAT)	IP, UbA	WW 3 & 4	(Vina-Vilaseca and Sorkin, 2010)
	Endosomal sorting complex required for transport complex-I subunit TSG101	IF, IP, UbA		(Chung et al., 2008)
	Epithelial sodium channel (ENaC)	IP, PD, SPR, UbA	WW 3 & 4	(Asher et al., 2003; Bhalla et al., 2006; Kamynina et al., 2001a; Kamynina et al., 2001b; Lagnaz et al., 2014; Sanchez-Perez et al., 2007; Snyder et al., 2004; Wiemuth et al., 2010; Zhou et al., 2007)
	Feline immunodeficiency virus gag (FIV Gag)	IP, UbA		(Calistri et al., 2009)
	GluA1 subunit of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR)	IP, UbA		(Jewett et al., 2015; Lee et al., 2018; Zhu et al., 2017)
	G-protein-coupled receptor kinase 2 (GRK2)	IP, Phos	WW 1 & 2	(Sanchez-Perez et al., 2007)
	G-protein coupled receptor protease-activated receptor-1 (PAR1)	IF, UbA		(Grimsey et al., 2018)
	Growth factor receptor-bound protein 10 (Grb10)	IP		(Velez et al., 2016)
	H ⁺ /Cl ⁻ exchange transporter 5 (CIC-5)	IP, PD, UbA		(Hryciw et al., 2004)
	High affinity choline transporter 1 (CHT1, SLC5A7)	IP, UbA		(Yamada et al., 2012)
	Human immunodeficiency virus gag (HIV Gag)	IP, UbA	C2	(Usami et al., 2008)
	Human organic anion transporter 1 (hOAT1)	IP, WB		(Xu et al., 2016b)
	Human organic anion transporter 3 (hOAT3)	IP		(Xu et al., 2016a)
	Human organic anion transporter 4 (hOAT4)	IP		(Wang et al., 2016a)
	Inhibitor of nuclear factor kappa-B kinase subunit beta (IKK β)	IP, Phos		(Edinger et al., 2009)
	Interleukin-2 receptor γ (IL-2R)	IP, MS		(Malarde et al., 2009)
	Large neutral amino acids transporter small subunit 1 (LAT1, 4F2LC)	UbA		(Rosario et al., 2016)

Low-density-lipoprotein receptor class A domain-containing protein 3 (LRAD3)	IP, MS	WW 1-4	(Noyes et al., 2016)
Multivesicular bodies 12B (MVB12B, FAM125B)	IP, UbA		(Chung et al., 2008)
Na ⁺ /Cl ⁻ cotransporter (NCC)	IP		(Lagnaz et al., 2014)
Na ⁺ /H ⁺ exchanger 3 (NHE3)	IP, UbA		(No et al., 2014)
Nedd4 WW domain-binding protein 5 (N4WBP5, NDFIP1)	FW, IP, UbA	WW 1-4	(Fotia et al., 2006; Konstas et al., 2002)
Neurogenic locus notch homolog protein 1 (Notch1)	IP, UbA		(Guarnieri et al., 2018)
Neurotrophic tyrosine kinase receptor type 1 (TrkA)	IP, UbA	WW 3	(Anta et al., 2016)
Niemann-Pick disease type C2 protein intracellular cholesterol transporter 2 (NPC2)	2H, IP	C2	(Araki et al., 2009)
Occludin	IP, UbA, WB		(Raikwar et al., 2010)
Pak-interacting exchange factor β-Pix	WB, IP		(Ho et al., 2018)
Parainfluenza virus 5 non-structural protein V (PIV5)	IP		(Ray et al., 2019)
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA)	IP, UbA		(Wang et al., 2016b)
Phosphorylated tyrosine-protein kinase SYK (p-Syk, spleen tyrosine kinase)	IP, WB		(Yip et al., 2016)
Potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel (HCN1)	IF, IP		(Wilkars et al., 2014)
Potassium voltage-gated channel subfamily A member 3 (KCNA3, Kv1.3)	IP		(Velez et al., 2016)
Potassium voltage-gated channel subfamily H member 2 (KCNH2, hERG)	IF, IP		(Guo et al., 2012)
Potassium voltage-gated channel subfamily KQT member 1 (KCNQ1, Kv7.1)	IP, UbA		(Alzamora et al., 2010; Andersen et al., 2015)
Potassium voltage-gated channel subfamily KQT member 2 (KCNQ2)	IF, IP, PD, UbA		(Ekberg et al., 2007)
Potassium voltage-gated channel subfamily KQT member 3 (KCNQ3)	IP, PD, UbA		(Ekberg et al., 2007)
Proto-oncogene tyrosine-protein kinase Src (c-Src)	IP		(Grimsey et al., 2018)
Serine/threonine-protein kinase WNK3 (WNK3)	IP, MS		(Lagnaz et al., 2014)
Serine/threonine-protein kinase Sgk1 (SGK1)	IF, Phos, SPR	WW 3	(Al-Qusairi et al., 2016; Asher et al., 2003; Gao et al., 2009)
Serum and glucocorticoid-regulated kinase 1 (SGK1)	IP, PD, Phos, SPR, WB	WW 2 & 3	(Dieter et al., 2004; Wiemuth et al., 2010)
Serum and glucocorticoid-regulated kinase 1 (SGK3)	Phos, WB		(Dieter et al., 2004)
Ski-related novel protein N (SnoN)	IP		(Kuratomi et al., 2005)
SMAD family member2 (Smad2)	IP, ITC, PD, UbA		(Gao et al., 2009; Kuratomi et al., 2005)
SMAD family member3 (Smad3)	IP, ITC, PD, UbA		(Gao et al., 2009; Kuratomi et al., 2005)
SMAD family member6 (Smad6)	IP		(Kuratomi et al., 2005)
SMAD family member7 (Smad7)	2H, IF, IP		(Kuratomi et al., 2005)
Sodium-coupled neutral amino acid transporter 2 (SNAT2, ATA2)	IF, IP, UbA		(Hatanaka et al., 2006; Rosario et al., 2016)
Sodium-dependent glutamate/aspartate transporter 2 (SLC1A2, GLT-1)	IF, IP, UbA		(Garcia-Tardon et al., 2012; Zhang et al., 2017b)
Surfactant protein C (SP-C)	IP, WB		(Kotorashvili et al., 2009)
Thioredoxin-like protein 1 (TXNL1, TRP32)	IP, UbA		(Farris et al., 2017)
Transforming growth factor-β type I receptor (TGF-β1, TβR-1)	IP, UbA		(Kuratomi et al., 2005)
Transient receptor potential cation channel subfamily V member 6 (TRPV6)	IF, IP, PD, UbA	WW 1 & 2	(Zhang et al., 2010b)
Tweety family member 1 (TTYH1)	IP, UbA		(He et al., 2008)
Tweety family member 2 (TTYH2)	IF, IP, PD, UbA		(He et al., 2008)
Tweety family member 3 (TTYH3)	IP, UbA		(He et al., 2008)
Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Fotia et al., 2006)
Ubiquitin-conjugating enzyme E3 D2 (UBE2D2, UBCH5B)	UbA		(Fotia et al., 2006)
Ubiquitin-conjugating enzyme E3 D3 (UBE2D3, UBCH5C)	UbA		(Wang et al., 2016b)
Ubiquitin-conjugating enzyme E2 E3 (UBE2E3)	2H, IP, PD, UbA		(Debonneville and Staub, 2004)
Ubiquitin-conjugating enzyme E3 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Fotia et al., 2006)
Ubiquitin-specific protease 36 (USP36)	IP, PD	WW 1, 3 & 4	(Anta et al., 2016)
Voltage-gated sodium channel protein type 5 subunit alpha (Nav 1.5)	IF, IP, UbA		(Luo et al., 2017)
Voltage-gated sodium channel protein type 9 subunit alpha (Nav 1.7)	PD, UbA		(Laedermann et al., 2013)
Voltage-gated sodium channel protein type 10 subunit alpha (Nav 1.7)	PD		(Laedermann et al., 2013)
SMAD specific E3 ubiquitin	1-phosphatidylinositol 4,5-bisphosphate phosphodiesterase gamma-1 (PLCγ)	IF, IP	(Wang et al., 2003)

protein ligase 1 (SMURF1, SMAD ubiquitination regulatory factor 1) Gene: SMURF1 Chromosome location: 7q22.1 Ubiquitin Linkages: K29, K48	Axis inhibition protein 1 (Axin-1)	IP, PD, MS, UbA		(Fei et al., 2013)
	Beta-transducin repeat-containing E3 ubiquitin ligase (β TrCp, BTRC)	IF, IP, UbA	HECT	(Zhang et al., 2017c)
	Casein kinase-2 interacting protein-1 (CKIP-1, JBP, PLEKHO1)	IF, IP, PD, UbA	WW linker (268-282aa)	(Lu et al., 2008; Xie et al., 2011)
	Dishevelled-2 (Dvl2)	IP		(Narimatsu et al., 2009)
	Estrogen receptor α (ESR1, ER α)	IF, IP, PD, UbA	HECT	(Yang et al., 2018)
	Ephrin-B1 (EFL-3, ELK-L)	IP, UbA		(Hwang et al., 2013)
	Exportin-1 (Exp1, CRM1)	IF, IP	HECT NES (606-614aa)	(Tajima et al., 2003)
	F-box and LRR domain-containing protein 15 (FBXL15)	2H, IP, PD, UbA	HECT N-lobe (373-539aa)	(Cui et al., 2011)
	GLI-similar 3 (Glis3, ZNF515)	2H, IP, MS, TAP	WW 1 & 2	(ZeRuth et al., 2015)
	Inhibitor of growth protein 2 (ING2, p32)	IP, PD, UbA	HECT	(Nie et al., 2010a)
	Kruppel-like factor (KLF2, LKLF)	2H, IF, IP, PD, UbA	WW 1 & 2 (146-351aa)	(Xie et al., 2011)
	MAPK/ERK kinase kinase 2 (MEKK2, MAP3K2, MAPKKK2)	2H, IP, UbA	WW 1 & 2 (146-351 aa)	(Yamashita et al., 2005)
	Mitochondrial antiviral-signaling protein (MAVS, Cardiff, VISA)	IP, UbA		(Wang et al., 2012b)
	Myeloid differentiation primary response protein MyD88	IF, IP, UbA		(Lee et al., 2011b)
	NEDD4 family-interacting protein 1 (Ndfip1, N4WPB5)	IP, UbA		(Wang et al., 2012b)
	Neural precursor cell expressed developmentally downregulated protein 8 (NEDD8)	2H, IP, PD, UbA	WW 1 & 2, HECT	(Xie et al., 2014)
	Nuclear factor 1 C-type (NFI-C, CTF)	IP, UbA		(Lee et al., 2011a)
	Partitioning defective 6 homolog protein α (Par6)	IF, IP, UbA		(Cheng et al., 2011; Ozdamar et al., 2005)
	Proteasome activator REG γ (REG γ)	2H, IP, PD	WW 1 & 2	(Nie et al., 2010b)
	RAC-alpha serine/threonine-protein kinase (PKB, Akt)	IP		(Choi et al., 2014)
	Rho guanine nucleotide exchange factor 9 (Cdc42, PEM-2 homolog, ARHGEF9)	IP, PD, UbA	C2	(Yamaguchi et al., 2008)
	Runt-related transcription factor 2 (RUNX2, CBFA1)	IP, UbA		(Lu et al., 2011; Shen et al., 2006; Zhao et al., 2003)
	Securin (PTTG1)	IF, IP, UbA	HECT	(Wei et al., 2017)
	Signal transducer and activator of transcription 1 (STAT1)	IP, UbA	WW 1 & 2 (119-354aa)	(Yuan et al., 2012)
	SMAD family member 1 (Smad1)	2H, IP, UbA	WW 1 & 2 (146-351 aa)	(Yamashita et al., 2005; Zhao et al., 2003; Zhu et al., 1999)
	SMAD family member 4 (Smad4)	IF, IP, UbA		(Moren et al., 2005; Xie et al., 2014)
	SMAD family member 5 (Smad5)	IP, UbA		(Lu et al., 2011; Lu et al., 2008; Nie et al., 2010b; Zhu et al., 1999)
	SMAD family member 6 (Smad6)	IP, UbA		(Ebisawa et al., 2001; Lee et al., 2011b; Shen et al., 2006)
	SMAD family member 7 (Smad7)	2H, FBA, IF, IP, ITC, NMR, UbA	WW 2	(Aragon et al., 2012; Chong et al., 2010; Ebisawa et al., 2001; Suzuki et al., 2002; Tajima et al., 2003; Xie et al., 2014; Yamashita et al., 2005)
	SMAD specific E3 ubiquitin protein ligase 2 (SMURF2)	IP, UbA		(Fukunaga et al., 2008)
	TNF receptor-associated factor 1 (TRAF1, EB16)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010)
	TNF receptor-associated factor 2 (TRAF2, TRAP3)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010)
	TNF receptor-associated factor 3 (TRAF3, CAP1, CRAF1)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010)
	TNF receptor-associated factor 4 (TRAF4, CART1, MLN62, RNF83)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010; Zhang et al., 2013b)
	TNF receptor-associated factor 5 (TRAF5, RNF84)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010)
	TNF receptor-associated factor 6 (TRAF6, RNF85)	2H, IP, UbA	WW 1 & 2	(Li et al., 2010)
	Transcription factor jun-B (JUNB)	IP, PD, UbA		(Zhao et al., 2010)
	Transforming growth factor- β type 1 receptor (T β R-1)	IF, IP		(Ebisawa et al., 2001; Ozdamar et al., 2005)
	Transforming protein RhoA (RhoA)	IP, PD, UbA		(Cheng et al., 2011; Lu et al., 2011; Sahai et al., 2007; Wang et al., 2003; Wei et al., 2017)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Kristariyanto et al., 2015)

	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA		(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	PD, UbA		(Cui et al., 2011; Guo et al., 2011; Kristariyanto et al., 2015; Nie et al., 2010a; Xie et al., 2014; Yamashita et al., 2005)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Kristariyanto et al., 2015; Xie et al., 2014)
	Ubiquitin-conjugating enzyme E2 M (UBE2M, UBC12)	IP, PD, UbA	HECT	(Xie et al., 2014)
	Wolframin (WFS1)	2H, IF, IP, PD, UbA	WW 1 & 2 (236-340aa)	(Guo et al., 2011)
	Zinc finger protein GLI-similar 3 (GLIS3)	2H, IP, UbA	WW 1-3 (199-383aa)	(ZeRuth et al., 2015)
SMAD specific E3 ubiquitin protein ligase 2 (SMURF2 ; SMAD ubiquitination regulatory factor 2) Gene: <i>SMURF2</i> Chromosome location: 17q23.3-q24.1 Ubiquitin Linkages: K48	150 kDa TGFβ-1 binding protein (CD109, CPAMD7)	IF, IP		(Biset et al., 2012)
	Aminoacyl tRNA synthase complex-interacting multifunctional protein 1 (AIMP1, p43)	IF, IP, UbA	WW 1-3	(Lee et al., 2008b)
	Aminoacyl tRNA synthase complex-interacting multifunctional protein 2 (AIMP2, p38)	IF, IP, PD, UbA	HECT	(Kim et al., 2016a)
	Axis inhibition protein 1 (Axin-1)	IP, MS, PD, UbA		(Fei et al., 2013; Kim and Jho, 2010)
	Associated molecule with the SH3 of STAM (AMSH, STAMBPP)	IP, UbA		(Li and Seth, 2004)
	cAMP-specific 3',5'-cyclic phosphodiesterase 4B (PDE4B)	IP, PD, UbA	WW 1-3 (157-330aa)	(Cai et al., 2018)
	Connector enhancer of kinase suppressor of ras 2 (CNKSR2, CNK2)	IF, IP, SPR, UbA		(David et al., 2018)
	Deleted in azoospermia-associated protein 2 (DAZAP2, KIAA0058)	PD	WW 1-3	(Popova et al., 2012)
	Dishevelled-2 (Dvl2)	IP, UbA		(Narimatsu et al., 2009)
	DNA topoisomerase IIα (Topollα, TOP2A)	IF, IP, MS, PD PLA, UbA		(Emanuelli et al., 2017)
	Enhancer of zeste homolog 2 (EZH2, ENX1, KMT6)	IP, UbA		(Yu et al., 2013)
	Ephrin-B1 (EFL-3, ELK-L)	IP, UbA	WW 1-3	(Hwang et al., 2013)
	Epidermal growth factor receptor (EGFR)	IP, PD, UbA		(Ray et al., 2011)
	Exportin-1 (CRM1, XPO1)	IP, PD		(Kim et al., 2016a)
	F-box/LRR-repeat protein 15 (FBXL15)	IF, IP, PD, UbA	HECT	(Cui et al., 2011)
	F-box/WD repeat-containing protein 1A (β-TrCP1)	UbA		(Shukla et al., 2014)
	GLI-similar 3 (Glis3, ZNF515)	2H, IP, MS, TAP	WW 1-3	(ZeRuth et al., 2015)
	Glycogen synthase kinase-3 β (GSK3β)	IP, UbA		(Wu et al., 2009)
	Heat shock protein 27 (HSP27, HSPB1)	IF, IP		(Sun et al., 2011)
	Human Herpes Virus protein U24	ITC, NMR, PD	WW 3	(Sang et al., 2017)
	Inhibitor of differentiation 1 (ID1, BHLHB24)	IP, UbA	C2, WW 1-3	(Kong et al., 2011)
	Interleukin-25 (IL-25, IL-17E)	IP		(Zepp et al., 2015)
	Kruppel-like factor 5 (KLF5, BTEB2)	2H, IF, IP, UbA		(Du et al., 2011)
	Mitochondrial antiviral-signaling protein (MAVS, Cardiff, VISA)	IP, UbA		(Pan et al., 2014)
	Mitotic spindle assembly checkpoint protein MAD2A (MAD2, MAD2L1)	IP, UbA		(Osmundson et al., 2008)
	μ-type opioid receptor (MOR1, MOP)	IF, IP, UbA		(Dong et al., 2019)
	Myeloid differentiation primary response protein MyD88	IP, UbA		(Lee et al., 2011b)
	Neural precursor cell expressed developmentally downregulated protein 8 (NEDD8)	IF, IP, PD, UbA	HECT	(He et al., 2017; Shu et al., 2016)
	Neural precursor cell expressed developmentally downregulated protein 9 (NEDD9)	IP, UbA		(Moore et al., 2010)
	Nuclear factor 1 C-type (NFI-C. CTF)	IP, UbA		(Lee et al., 2011a)
	Patched-1 (Ptch1)	IF, IP, PD, UbA	WW 1-3	(Fleet et al., 2016; Huang et al., 2013; Yue et al., 2014)
	Papillomavirus minor capsid protein L1 (BPV1-L1)	IF, IP		(Dabydeen and Meneses, 2011)
	Papillomavirus minor capsid protein L2 (BPV1-L2)	IF, IP		(Dabydeen and Meneses, 2011)
	Partitioning defective 6 (Par6, TIP-40)	IP, UbA		(Narimatsu et al., 2009)
	Prickle-like protein 1 (Pk1)	IP, UbA		(Narimatsu et al., 2009)
	RAC-alpha serine/threonine-protein kinase (PKB, Akt)	IP, UbA		(Choi et al., 2014)
	RING finger protein 11 (RNF11)	IP, PD, UbA	WW 2 & 3	(Li and Seth, 2004; Malonis et al., 2017; Subramaniam et al., 2003)

WW domain containing E3 ubiquitin protein ligase 1 (WWP1, AIP5, Tiul1, Hsdrp1) Gene: WWP1 Chromosome location: 8q21.3 Ubiquitin Linkages: K63	RING finger LIM-binding protein (RLIM, RNF12)	IF, IP, PD	(Huang et al., 2011)
	RING finger protein 20 (RNF20, BRE1A)	IF, IP, PD, Uba	(Blank et al., 2012)
	Runt-related transcription factor 2 (RUNX2, CBFA1)	IP	(Choi et al., 2014)
	Ski oncogene (c-Ski)	IP, Uba	(Zhou et al., 2017a)
	Ski-related oncogene (SnoN, SKIL)	IP, Uba	(Bonni et al., 2001; Mizuide et al., 2003)
	SMAD family member 1 (Smad1)	2H, PD, Uba	WW 2 & 3 (Lin et al., 2000; Zhang et al., 2001)
	SMAD family member 2 (Smad2)	2H, IP, PD, Uba	WW 2 & 3 (Bonni et al., 2001; Lin et al., 2000; Mizuide et al., 2003; Runyan et al., 2009; Tang et al., 2011; Zhang et al., 2001; Zhou et al., 2017a)
	SMAD family member 3 (Smad3)	2H, IP, FP, ITC, PBA, PD, Uba	WW 2 & 3 (Bonni et al., 2001; Schiro et al., 2011; Xu et al., 2017; Zhang et al., 2001) Lin et al., 2000; Tang et al., 2011; Wu et al., 2008)
	SMAD family member 3 (Smad4)	IP, Uba	(Moren et al., 2005; Zhou et al., 2017a)
	SMAD family member 7 (Smad7)	FBA, IF, IP, ITC, NMR, PD, Uba	WW 3 (Aragon et al., 2012; Bizet et al., 2012; Chong et al., 2006; Chong et al., 2010; Ganji et al., 2015; Kavsak et al., 2000; Kim et al., 2016a; Lee et al., 2008b; Ogunjimi et al., 2005; Tang et al., 2008; Wiesner et al., 2007)
	SMAD specific E3 ubiquitin protein ligase 1 (SMURF1)	IP, Uba	(Fukunaga et al., 2008)
	TNF receptor-associated factor 2 (TRAF2)	2H, IP, Uba	C2 & HECT (Carpentier et al., 2008)
	TNF receptor-associated factor 4 (TRAF4, RNF68)	2H, IP, Uba	(Zepp et al., 2015; Zhang et al., 2013b)
	Transcription factor Yin and Yang 1 (YY1, INO80S)	IP, PD, Uba	WW 1-3 (Jeong et al., 2014; Ramkumar et al., 2013)
	Transforming growth factor-β type 1 receptor (TβR-1)	IF, IP, Uba	(Bizet et al., 2012; Bonni et al., 2001; Kavsak et al., 2000; Yang et al., 2009; Zhang et al., 2013b)
	Transforming growth factor-β type 2 receptor (TβR-2)	IF, IP, Uba	(Kavsak et al., 2000; Lee et al., 2008b; Zhang et al., 2013b)
	Transforming protein RhoA (RhoA)	Uba	(Wiesner et al., 2007)
	Tribbles homolog 3 (TRB3, SINK)	IP, Uba	(Hua et al., 2011)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	CE, MS, PD, Uba	(Kim and Jho, 2010; Kristariyanto et al., 2015; Shukla et al., 2014; Subramaniam et al., 2003; Wang et al., 2019)
	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	PD, Uba	(Kristariyanto et al., 2015; Subramaniam et al., 2003)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	PD, Uba	(Kim and Jho, 2010; Kristariyanto et al., 2015; Malonis et al., 2017; Subramaniam et al., 2003)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	PD, Uba	(Cui et al., 2011; Kristariyanto et al., 2015; Mari et al., 2014; Ogunjimi et al., 2005; Pan et al., 2014; Wiesner et al., 2007)
	Ubiquitin-conjugating enzyme E2 M (UBE2M, UBC12)	IP, Uba	HECT (Shu et al., 2016)
	Ubiquitin-like protein Nedd8 (NEDD8)	2H, IP, PD, Uba	WW 1 & 2, HECT (Xie et al., 2014)
	Zinc finger protein GLI-similar 3 (GLIS3)	2H, IP, Uba	WW 1-3 (143-334aa) (ZeRuth et al., 2015)
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Epidermal growth factor receptor 4 (HER4/ERBB4) Ezrin (Cytovillin, p81) HTLV-1 Gag polyprotein (Pr55Gag) Kruppel-like factor 2 (KLF2) Kruppel-like factor 5 (KLF5, BTEB2) RING finger protein 11 (RNF11, CGI-123) Runt-related transcription factor 2 (RUNX2)	Cellular tumor antigen p53 (p53, TP53)	IP, PD, Uba	(Laine and Ronai, 2007)
	Cellular tumor antigen p63 (p63, TP63)	IP, Uba	(Peschiaroli et al., 2010)
	Ebola virus VP40	CE, IF, IP, PD, Uba	WW 1 (Han et al., 2017)
	Epidermal growth factor receptor 4 (HER4/ERBB4)	IF, IP, PD, Uba	WW 1-4 (Feng et al., 2009; Li et al., 2009)
	Ezrin (Cytovillin, p81)	2H, IP, PD, Uba	WW 1 & 3 (Zaarour et al., 2012)
	HTLV-1 Gag polyprotein (Pr55Gag)	ELISA, IP, WB	WW 1-4 (Heidecker et al., 2007)
	Kruppel-like factor 2 (KLF2)	2H, IP, Uba	(Zhang et al., 2004)
	Kruppel-like factor 5 (KLF5, BTEB2)	IF, IP, PD, Uba	(Chen et al., 2005)
	RING finger protein 11 (RNF11, CGI-123)	2H, IF, IP, PD, Uba	WW 1 & 3 (Azmi and Seth, 2005; Chen et al., 2008)
	Runt-related transcription factor 2 (RUNX2)	IP, Uba	WW 1-4 (Jones et al., 2006; Shu et al., 2013)

Serine/threonine-protein kinase LATS1 (LATS1, WARTS)	IP, PD, UbA	WW 1-3	(Yeung et al., 2013)
SMAD family member 1 (Smad1)	IP		(Komuro et al., 2004)
SMAD family member 2 (Smad2)	CE, IP, UbA		(Komuro et al., 2004; Seo et al., 2004)
SMAD family member 3 (Smad3)	IP		(Komuro et al., 2004; Seo et al., 2004)
SMAD family member 4 (Smad4)	IP		(Komuro et al., 2004)
SMAD family member 6 (Smad6)	IP, UbA		(Komuro et al., 2004; Seo et al., 2004)
SMAD family member 7 (Smad7)	2H, IF, IP, PD, UbA		(Courivaud et al., 2015; Komuro et al., 2004; Seo et al., 2004)
Spartin (SPG20, SPART)	2H, IF, IP, MS, TAP, UbA	WW 1-4	(Eastman et al., 2009; Milewska et al., 2009)
TGF β receptor type-1 (T β R1, ALK-5)	2H, CE, IP, UbA	C2	(Komuro et al., 2004; Seo et al., 2004)
Transcription factor jun-B (JUNB)	IP, UbA		(Zhao et al., 2011)
Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Kristariyanto et al., 2015; Wang et al., 2019)
Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA		(Kristariyanto et al., 2015)
Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA		(Kristariyanto et al., 2015)
Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Kristariyanto et al., 2015)
WW domain containing E3 ubiquitin protein ligase 2 (WWP2, AIP2)	CE, PD, UbA		(Chaudhary and Maddika, 2014)
WW domain containing E3 ubiquitin protein ligase 2 (WWP2, AIP2) Gene: <i>WWP2</i> Chromosome location: 16q22.1 Ubiquitin Linkages: K48, K63	Atrophin-1	2H, PD	(Wood et al., 1998)
	Cellular tumor antigen p73 (p73, TP73)	IP, PD, MS, TAP, UbA	(Chaudhary and Maddika, 2014)
	Dishevelled-2 (Dvl2)	IF, IP, MS, PD, UbA	C2, WW 1 & 2 (Mund et al., 2015)
	F-box and LRR domain-containing protein 15 (FBXL15)	IP, UbA	HECT N-lobe (Cui et al., 2011)
	GLI-similar 3 (Glis3, ZNF515)	2H, IP, MS, TAP	WW 1-4 (ZeRuth et al., 2015)
	Goosecoid (Gsc)	IF, IP, PD, UbA	WW 1-4 (Zou et al., 2011)
	Mediator of RNA polymerase II transcription subunit 25 (Med25)	2H, IP	N-term (1-525aa) (Nakamura et al., 2011)
	Nedd4-family interacting protein 1 (NDFIP1)	UbA	(Jiang et al., 2019)
	Neurogenic locus notch homolog protein 1 (NOTCH1, TAN1)	IP, PD, UbA	(Jung et al., 2014; Mund et al., 2015)
	Neurogenic locus notch homolog protein 2 (NOTCH2)	PD, UbA	(Mund et al., 2015)
	Neurogenic locus notch homolog protein 3 (NOTCH3)	IF, IP, PD, MS, UbA	WW 1-4 (Jung et al., 2014; Mund et al., 2015)
	Octamer binding transcription factor 4 (OCT4, POU5F1)	IP, MS, PD, UbA	WW 1-4 (Xu et al., 2004)
	Phosphatidylinositol 3,4,5-trisphosphate 3-phosphatase and dual-specificity protein phosphatase PTEN (PTEN, MMAC1, TEP1)	FP, IP, MS, PD, UbA	(Chen et al., 2016; Dempsey et al., 2018; Jiang et al., 2019; Maddika et al., 2011)
	Protein phosphatase 1G (PPM1G)	IP, PD	(Chaudhary and Maddika, 2014)
	Receptor tyrosine-protein kinase erbB-4 (ErbB4, HER4)	IP, MS	(Gilmore-Hebert et al., 2010)
	Runt-related transcription factor 2 (RUNX2)	IP, PD, UbA	WW 2-4 (Mokuda et al., 2019)
	Sequestosome-1 (SQSTM1, p62)	UbA	(Jiang et al., 2019)
	SMAD family member 2 (Smad2)	2H, IP, UbA	N-term (Soond and Chantry, 2011)
	SMAD family member 3 (Smad3)	2H, IP, UbA	WW 1 (Soond and Chantry, 2011)
	SMAD family member 7 (Smad7)	2H, IP, NMR, PD, UbA	WW 3 & 4 (Soond and Chantry, 2011; Wahl et al., 2019)
	TIR-domain-containing adapter-inducing interferon- β (TRIF, TICAM-1)	IP, MS, TAP, UbA	WW 2 (Yang et al., 2013)
	Transcription factor SOX-9 (Sox9)	IP	N-term (1-294aa) (Nakamura et al., 2011)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA	(Kristariyanto et al., 2015; Wang et al., 2019)
	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA	(Kristariyanto et al., 2015)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA	(Chen et al., 2017; Chen et al., 2016; Kristariyanto et al., 2015; Yang et al., 2013)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA	(Kristariyanto et al., 2015; Mund et al., 2015; Xu et al., 2019)

WW domain-binding protein 2 (WBP-2)	UbA		2004)
WW domain containing E3 ubiquitin protein ligase 1 (WWP1, AIP5, Tiul1, Hsdrp1)	CE, PD, UbA		(Jiang et al., 2019) (Chaudhary and Maddika, 2014)
Zinc finger protein GLI-similar 3 (GLIS3)	2H	WW 1-3 (395-696aa)	(ZeRuth et al., 2015)

Detection methods: **2H**, yeast or mammalian-two hybrid; **CE**, co-elution during chromatography purification; **DeUbA**, *in vivo* or *in vitro* deubiquitylation assay; **ELISA**, enzyme-linked immunosorbent assay; **FBA**, *in vitro* filter binding assay; **FP**, fluorescence polarization; **FRET**, fluorescence resonance energy transfer; **FW**, far western immunoblot; **IF**, immunofluorescence; **IP**, immunoprecipitation; **ITC**, isothermal calorimetry; **MS**, liquid chromatography or MALDI MS/MS; **Native-PAGE**, non-denaturing polyacrylamide gel electrophoresis; **NMR**, nuclear magnetic resonance; **PD**, pulldown using GST, His or MBP tag; **PepA**, peptide array assay; **Phos**, *in vitro* phosphorylation; **SPR**, surface plasmon resonance; **TAP**, tandem affinity purification; **UbA**, ubiquitylation assay; **WB**, immunoblot; **X-ray**, X-ray crystallography.

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Table S3. Observed protein–protein interactions with HERC family HECT E3 ubiquitin ligases

HECT E3 Ubiquitin Ligase (E.C.: 2.3.2.26)	Interacting protein	Detection Method	Region of interaction	References
HECT domain and RCC1-like domain-containing protein 1 (HERC1, p532, p619, MDFPMR) Gene: <i>HERC1</i> Chromosome location: 15q22.31 Ubiquitin Linkages: K48	ADP-ribosylation factor 1 (ARF1)	IP, WB	RLD2	(Rosa et al., 1996)
	ADP-ribosylation factor 6 (ARF6)	GNBA	RLD1	(Garcia-Gonzalo et al., 2005)
	BCL-2-antagonist/killer (BAK, BCL2L7, CDN1)	IF, PLISA	BH3	(Holloway et al., 2015)
	Clathrin heavy chain (CHC)	2H, IP, PD	RLD2	(Rosa and Barbacid, 1997)
	Heat shock protein 80 (HSP70)	IP		(Rosa and Barbacid, 1997)
	M2-pyruvate kinase	2H, IF, PD	HECT	(Garcia-Gonzalo et al., 2003)
	RAF proto-oncogene serine/threonine-protein kinase (C-RAF, RAF1)	IP, PD, Uba	N-term (1-412aa)	(Schneider et al., 2018)
	Tuberous sclerosis complex 2 (TSC2, Tuberin)	IP, MS	C-term (3901-4861aa)	(Chong-Kopera et al., 2006)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	Uba		(Schwarz et al., 1998)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	Uba		(Schwarz et al., 1998)
HECT domain and RCC1-like domain-containing protein 2 (HERC2) Gene: <i>HERC2</i> Chromosome location: 15q22.31 Ubiquitin Linkages: K48, K63	Aurora kinase B (AURKB, AIM-1, ARK2)	IP, MS	1-1000aa	(Galligan et al., 2015)
	Breast cancer type 1 susceptibility protein (BRCA1, RNF53)	IP, MS, Uba	HECT (4252-4834aa)	(Wu et al., 2010)
	cAMP-dependent protein kinase type II-beta regulatory subunit (PRKAR2B)	IP, MS	2600-3600aa	(Galligan et al., 2015)
	Carnitine O-palmitoyltransferase 1A (CPT1A, CPT1-L)	IP, MS	1-1000aa	(Galligan et al., 2015)
	Cellular tumor antigen p53 (p53, TP53)	IP, PD	CPH (2547-2640aa)	(Cubillos-Rojas et al., 2014)
	Centriolar coiled-coil protein 110 (CP110)	IP, MS		(Al-Hakim et al., 2012)
	Coatomer subunit epsilon (COPE, Epsilon-COP)	IP, MS	1700-2700aa	(Galligan et al., 2015)
	Coatomer subunit zeta-1 (COPZ1, Zeta-1 COP)	IP, MS	1700-2700aa	(Galligan et al., 2015)
	Crossover junction endonuclease MUS81 (MUS81)	IP, MS	1-1000aa	(Galligan et al., 2015)
	E6-associated protein (E6AP, UBE3A)	2H, CE, IF, IP, MS, PD, Uba	RLD2	(Galligan et al., 2015; Kuhnle et al., 2011; Kuhnle et al., 2018; Martinez-Noel et al., 2012; Martinez-Noel et al., 2018)
	Essential meiotic endonuclease 1 (EME1, MMS4, SLX2)	IP, MS	1-1000aa	(Galligan et al., 2015)
	Eukaryotic translation initiation factor 3 subunit E (EIF3E)	IF, IP, MS	3550-4500aa	(Galligan et al., 2015)
	Eukaryotic translation initiation factor 3 subunit H (EIF3H)	IP, MS	3550-4500aa	(Galligan et al., 2015)
	Eukaryotic translation initiation factor 3 subunit M (EIF3M)	IP, MS	3550-4500aa	(Galligan et al., 2015)
	Ferritin heavy chain (FTH1, Ferritin H subunit)	IP, MS	1700-2700aa	(Galligan et al., 2015)
	Ferritin light chain (FTL, Ferritin L subunit)	IP, MS	1700-2700aa	(Galligan et al., 2015)
	HLA class I histocompatibility antigen, A-2 alpha chain (HLA-A)	IP, MS	950-1750aa	(Galligan et al., 2015)
	Kinesin-like protein KIF20A (KIF20A, MKLP2, RAB6KIFL)	IP, MS	1-1000aa	(Galligan et al., 2015)
	Minor histocompatibility antigen H13 (HM13, IMP-1)	IP, MS	950-1750aa	(Galligan et al., 2015)
	Neuralized-like protein 4 (NEURL4)	IP, MS, TAP, Uba		(Al-Hakim et al., 2012; Galligan et al., 2015)
	Nuclear distribution gene C-like protein 2 (NudCL2)	IP, MS		(Li et al., 2019)
	Phosphorylase b kinase gamma catalytic chain (PHKG2, PHK-gamma-LT)	IP, MS	3550-4500aa	(Galligan et al., 2015)
	Phosphorylase b kinase regulatory subunit beta (PHKB)	IP, MS	3550-4500aa	(Galligan et al., 2015)
	Protein bicaudal D homolog 2 (BICD2, KIAA0699)	IP, MS	2600-3600aa	(Galligan et al., 2015)
	Replication factor A protein 2 (RPA2, RP-A p32)	IP, PD, Uba	HECT	(Lai et al., 2019)
	RING-type E3 ubiquitin ligase PIAS4 (PIAS4)	IP, PD		(Danielsen et al., 2012)
	RING-type E3 ubiquitin ligase RNF8 (RNF8)	IP, MS	HECT (4421-4834aa)	(Bekker-Jensen et al., 2010; Danielsen et al., 2012)
	RING-type E3 ubiquitin ligase RNF168 (RNF168)	PD		(Bekker-Jensen et al., 2010)
	Small ubiquitin-related modifier 1 (SUMO1)	IP, ITC, PD	ZZ (2702-2755aa)	(Danielsen et al., 2012)

	Squalene synthase (SQS, FDFT1)	IP, MS	1-1000aa	(Galligan et al., 2015)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA		(Kang et al., 2010)
	Ubiquitin-conjugating enzyme E3 D3 (UBE2D3, UBCH5C)	UbA		(Al-Hakim et al., 2012)
	WD repeat-containing protein Monad (WDR92)	IP, MS	1700-2700aa	(Galligan et al., 2015)
	Xeroderma pigmentosum group A-complementing protein (XPA)	IP, MS, UbA		(Kang et al., 2010)
	Zinc finger FYVE domain-containing protein 9 (ZFYVE9, NSP, SARA)	IP, MS	2600-3600aa	(Galligan et al., 2015)
HECT domain and RCC1-like domain-containing protein 3 (HERC3) Gene: <i>HERC3</i> Chromosome location: 4q22.1 Ubiquitin Linkages: K48	26S proteasome non-ATPase regulatory subunit 2 (PSMD2, TRAP2, RPN1)	IP, MS		(Hochrainer et al., 2015)
	26S proteasome non-ATPase regulatory subunit 4 (PSMD4, RPN10, S5A)	IP, MS		(Hochrainer et al., 2015)
	26S proteasome regulatory subunit 7 (PSMC2, LCMSS1, RPT1)	IP, MS		(Hochrainer et al., 2015)
	26S proteasome regulatory subunit 6B (PSMC4, TBP7, MIP224)	IP, MS		(Hochrainer et al., 2015)
	26S proteasome regulatory subunit 8 (PSMC5, SUG1, TRIP1)	IP, MS		(Hochrainer et al., 2015)
	HECT domain and RCC1-like domain-containing protein 6 (HERC6)	IF, IP		(Hochrainer et al., 2008)
	Proteasome subunit alpha type-4 (PSMA4, HC9, PSC9)	IP, MS		(Hochrainer et al., 2015)
	Transcription factor p65 (RELA, NFKB3)	IF, IP, MS		(Hochrainer et al., 2015)
	Ubiquilin-1 (UBQLN1, hPLIC-1)	2H, IP, MS	HECT	(Hochrainer et al., 2008; Hochrainer et al., 2015)
	Ubiquilin-2 (UBQLN2, hPLIC-2)	2H, IF, IP, UbA	HECT	(Hochrainer et al., 2008)
HECT domain and RCC1-like domain-containing protein 4 (HERC4) Gene: <i>HERC4</i> Chromosome location: 10q21.3 Ubiquitin Linkages: K48	Serine/threonine-protein kinase LATS1 (LATS1, WARTS)	IP, PD, UbA		(Xu et al., 2019)
	Scaffold protein salvador (Sav, SHRP)	IP, UbA	RLD	(Aerne et al., 2015)
	Transcription factor Maf (c-Maf)	CE, IF, IP, MS, UbA		(Zhang et al., 2016)
HECT domain and RCC1-like domain-containing protein 5 (HERC5, Cyclin-E-binding protein, CEB1, CEBP1) Gene: <i>HERC5</i> Chromosome location: 4q22.1 Ubiquitin Linkages: N/A ISG15-specific	HIV-1 Gag polyprotein (Pr55Gag)	IF, IP, MS, ISGylA		(Woods et al., 2011)
	MLV Gag polyprotein (Pr65Gag)	ISGylA		(Woods et al., 2011)
	Heat shock cognate 71 kDa protein (Hsc70, LAP-1)	IP		(Wong et al., 2006)
	Interferon-stimulated gene 15 (ISG15)	ISGylA		(Dastur et al., 2006; Wong et al., 2006; Woods et al., 2011)
	NS1 protein of influenza A virus (NS1A)	IP, ISGylA, PD	RLD	(Tang et al., 2010; Zhao et al., 2010)
	Nucleoside diphosphate kinase B (NDKB, Nm23B)	2H, IF, IP, UbA	HECT	(Hochrainer et al., 2008)
	Ras-related nuclear protein (GTPase Ran, ARA24)	IP, PD		(Woods et al., 2014)
	Serine/threonine-protein kinase 38 (STK38)	IP, PD		(Takeuchi et al., 2006)
	Regulator of G-protein signaling 3 (RGS3)	IP, PD		(Takeuchi et al., 2006)
	Thioredoxin reductase (TR)	IP, PD		(Wong et al., 2006)
	α -tubulin	IP, PD		(Takeuchi et al., 2006)
	Ubiquitin-conjugating enzyme E2 L6 (UBE2L6, UBCH8, RIG-B)	ISGylA		(Takeuchi et al., 2006; Woods et al., 2011; Woods et al., 2014; Zhao et al., 2004)
HECT domain and RCC1-like domain-containing protein 6 (HERC6) Gene: <i>HERC6</i> Chromosome location: 4q22.1 Ubiquitin Linkages: N/A ISG15-specific	Xeroderma pigmentosum group D (XPD)	IP, PD		(Takeuchi et al., 2006)
	HECT domain and RCC1-like domain-containing protein 3 (HERC3)	IF, IP		(Hochrainer et al., 2008)
	HECT domain and RCC1-like domain-containing protein 4 (HERC4)	IF, IP		(Hochrainer et al., 2008)
	Interferon-stimulated gene 15 (ISG15)	ISGylA		(Ketscher et al., 2012; Oudshoorn et al., 2012)
	Ubiquitin-conjugating enzyme E2 L6 (UBE2L6, UBCH8, RIG-B)	ISGylA		(Ketscher et al., 2012)

Detection methods: **2H**, yeast or mammalian-two hybrid; **CE**, co-elution during chromatography purification; **GNBA**, guanine nucleotide binding assay; **IF**, immunofluorescence; **IP**, immunoprecipitation; **ISGylA**, ISGylation assay; **MS**, liquid chromatography or MALDI MS/MS; **PLISA**, proximity ligation *in situ* assay; **PD**, pulldown using GST, His or MBP tag; **TAP**, tandem affinity purification; **UbA**, ubiquitylation assay; **WB**, immunoblot.

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Table S4. Observed protein-protein interactions with ‘Other’ HECT E3 ubiquitin ligases

HECT E3 Ubiquitin Ligase (E.C.: 2.3.2.26)	Interacting protein	Detection Method	Region of interaction	References
Apoptosis-Resistant E3	Serine protease HTRA2, mitochondrial (HtrA2, OMI, PRSS25)	2H, IP, Uba, WB		(Kim et al., 2013)
Ubiquitin Protein Ligase 1 (AREL1, KIAA0317)	Direct IAP-binding protein with low pI (DIABLO, SMAC)	2H, IP, Uba, WB		(Kim et al., 2013)
Gene: AREL1	Septin-4 (SEPT4), aka Apoptosis-related protein in the TGF-beta signaling pathway (ARTS)	2H, IP, Uba, WB		(Kim et al., 2013)
Chromosome location: 14q24.3	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	Uba		(Kim et al., 2013; Kristariyanto et al., 2015b)
Ub linkage types: K11, K29, K33	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	Uba		(Kristariyanto et al., 2015b)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	Uba		(Kristariyanto et al., 2015b; Michel et al., 2015)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	Uba		(Kristariyanto et al., 2015b)
G2/M Phase-Specific E3	Chromosome 2 open reading frame 29 (C2orf29)	2H		(Brooks et al., 2014)
Ubiquitin Protein Ligase 1 (G2E3, KIAA1333)	DAZ interacting protein 3 (DZIP3, hRUL138)	2H, PD		(Brooks et al., 2014)
Gene: G2E3	Eukaryotic initiation factor 3 subunit 4 (EIF3S4)	2H		(Brooks et al., 2014)
Chromosome location: 14q12	Inhibitor of CDK interacting with cyclin A1 (INCA1)	2H, PD		(Brooks et al., 2014)
Ub linkage types: K48	Proteasome subunit beta 4 (PSMB4)	2H, PD		(Brooks et al., 2014)
	Ribosomal protein 18 (RPL18)	2H		(Brooks et al., 2014)
	RING finger protein 138/ NLK associated RING finger (RNF138, NARF)	2H, PD, WB	N-term	(Brooks et al., 2014)
	Serine protease hepsin (HPN, TMPRSS1)	IP, MS, Uba		(Zhang et al., 2018)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	Uba, WB	HECT	(Brooks et al., 2008)
HECT Domain and Ankyrin Repeat-Containing E3	Beta-2 adrenergic receptor (β_2 AR)	IP, MS, WB		(Lachance et al., 2014)
Ubiquitin Protein Ligase 1 (HACE1, KIAA1320)	Optineurin (OPTN, FIP2)	2H, IP, PD	ANK domain	(Liu et al., 2014)
Gene: HACE1	Ras-related protein Rab-1A (Rab1A)	IP, MS, PD, WB		(Tang et al., 2011)
Chromosome location: 6q21	Ras-related protein Rab-4A (Rab4A)	IP, MS, PD, WB		(Tang et al., 2011)
Ub linkage types: K27, K48, K63	Ras-related protein Rab-6A (Rab6A)	MS, WB		(Lachance et al., 2014)
	Ras-related protein Rab-8A (Rab8A, c-mel)	MS, WB		(Lachance et al., 2014)
	Ras-related protein Rab-11A (Rab11A, YL8)	IP, MS, WB		(Lachance et al., 2014)
	Ras-related protein Rac1 (Rac1, RacA)	IP, PD, WB	ANK (Ankyrin repeat), HECT	(Acosta et al., 2018; Andrio et al., 2017; Castillo-Lluga et al., 2013; Daugaard et al., 2013; Torrino et al., 2011)
	Retinoic acid receptor beta (RAR β)	2H, IP, PD	C-term	(Zhao et al., 2009a)
	Tumor necrosis factor (TNF) receptor associated factor 2 (TRAF2)	Uba		(Tortola et al., 2016)
	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	Uba, UbSu		(Mulder et al., 2016)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	Uba	HECT	(Anglesio et al., 2004)
	Ubiquitin-conjugating enzyme E2 N (UBE2N, UBC13)	Uba	HECT	(Anglesio et al., 2004)
	Y-Box Binding Protein 1 (YB-1)	IP, Uba		(Palicharla and Maddika, 2015)
HECT Domain E3 Ubiquitin Protein Ligase 1 (HECTD1, KIAA1131)	Actin cross-linking family protein 7 (ACF7, MACF1)	IP, MS, PLA, WB		(Duhamel et al., 2018)
Gene: HECTD1	Adenomatous polyposis coli (APC)	IP, MS		(Tran et al., 2013)
Chromosome location: 14q12	ATP binding cassette sub-family A member 1 (ABCA1)	IP, MS, WB		(Aleidi et al., 2018)
Ub linkage types: K48, K63	Ubiquitin thiolesterase Trabid (Trabid, ZRANB1)	IP, MS, WB		(Oikonomaki et al., 2017; Tran et al., 2013)
	Heat shock protein 90 (Hsp90)	2H, IP, MS, WB		(Sarkar and Zohn, 2012)
	IQ Motif-Containing GTPase Activating Protein 1 (IQGAP1, p195)	IP, Uba, WB		(Shen et al., 2017)
	Phosphatidylinositol 4-phosphate 5-kinase type I γ (PIP5K, KIAA0589)	IP, WB		(Li et al., 2013a)
	Retinoic acid receptor alpha (RAR α)	2H, IP, WB	N-term	(Sugrue et al., 2019)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	Uba	HECT	(Duhamel et al., 2018)
	Ubiquitin thiolesterase 15 (USP15)	IP, MS, WB		(Oikonomaki et al., 2017)
HECT domain-containing protein 2 (HECTD2)	<i>Clostridium botulinum</i> neurotoxin catalytic light chain A (BoNT/A catalytic LCA)	IP, Uba		(Tsai et al., 2017)
Gene: HECTD2	Protein inhibitor of activated STAT protein 1 (PIAS1, GBP)	FRET, IP, Uba, WB		(Coon et al., 2015)

Chromosome location: 10q23.32 Ubiquitin Linkages: K48	Ubiquitin-conjugating enzyme E2-16 kDa (UBC5)	UbA		(Coon et al., 2015)
	Ubiquitin-conjugating enzyme E2-18 kDa (UBC7)	UbA		(Coon et al., 2015)
	Caspase-8 (CASP-8, MCH5)	IP, PD	DOC	(Li et al., 2013c)
HECT domain-containing protein 3 (HECTD3) Gene: HECTD3 Chromosome location: 1p34.1 Ub linkage types: K27, K29, K48, K63	Caspase-9 (CASP-9, MCH6)	PD, WB		(Li et al., 2017a)
	Heat shock protein 90 – Raf1 complex (Hsp90-CRAF)	IP, PLA, WB	DOC	(Li et al., 2017b)
	Mucosa-associated lymphoid tissue lymphoma translocation protein 1 (MALT1)	2H, IP, MS, PD, WB, UbA	DOC (216-393aa)	(Cho et al., 2019; Li et al., 2013b)
	Signal transducer and activator of transcription 3 (STAT3)	IP, MS, WB, UbA	DOC (110-397)	(Cho et al., 2019)
	Syntaxin-8 (STX8)	2H, IP		(Zhang et al., 2009)
	TRIO and F-actin-binding protein (TRIOBP, TARA)	2H, IP, PD, WB	N-term	(Yu et al., 2008)
	Tumor necrosis factor (TNF) receptor-associated factor 3 (TRAF3, CAP1, CRAF1)	IP, UbA		(Li et al., 2018)
	None reported			
HECT, Uba, and WWE Domain-Containing E3 Ubiquitin Protein Ligase 1 (HUWE1, UREB1, HECTH9, ARF-BP1, MULE, E3 Histone, LASU1, KIAA0312, KIAA1578) Gene: HUWE1 Chromosome location: Xp11.22 Ub linkage types: K6, K48, K63	Activating molecule in beclin1-regulated autophagy protein 1 (AMBRA1, KIAA1736)	IP, MS, UbA, WB		(Di Rita et al., 2018)
	Atonal homolog basic helix-loop-helix transcription factor 1 (ATOH1)	IP, MS, PLA, WB		(Cheng et al., 2016; Forget et al., 2014)
	ATP-binding cassette sub-family G member 1 (ABCG1, ABC8)	IP, MS, WB		(Aleidi et al., 2015)
	ATP-binding cassette sub-family G member 4 (ABCG4)	IP, MS, WB		(Aleidi et al., 2015)
	Breast cancer type 1 susceptibility protein (BRCA1, RNF53)	IF, IP, PD	2000-2364aa	(Wang et al., 2014)
	CCCTC-binding factor (CTCF, BORIS)	IP, WB	C-term (3674-4374aa)	(Qi et al., 2012)
	Cell division cycle protein 6 homolog (CDC6, CDC18L)	2H, IP, UbA, PD, WB	C-term (3987-4374aa)	(Hall et al., 2007)
	Cell division cycle-associated 7-like protein (CDCA7L, R1, RAM2, JPO2)	IP, UbA		(Lin et al., 2018)
	Cellular tumor antigen p53 (p53, TP53)	IP, MS, PD, WB	1015-4574aa	(Chen et al., 2005; Ma et al., 2016; Qi et al., 2012; Yang et al., 2018)
	Cullin-4B (CUL4B, KIAA0695)	IP, PD, UbA, WB	WWE, BH3 & 2000-2654aa	(Yi et al., 2015)
	Dishevelled (DVL)	IF, IP, MS, WB	C-term	(de Groot et al., 2014)
	DNA damage-binding protein 1 (DDB1, XAP1)	IP		(Yi et al., 2015)
	DNA damage-inducible transcript 4 protein (DDIT4, REDD1)	IP, MS, UbA		(Thompson et al., 2014)
	DNA polymerase λ (Pol λ)	IP, MS, UbA		(Markkanen et al., 2012)
	Growth arrest and DNA damage-inducible protein 45 beta (GADD45B, MYD118)	IF, IP, WB		(He et al., 2015)
	Glycine receptor subunit alpha-1 (GlyRs-α1, GLRA1)	IP, UbA, WB		(Zhang et al., 2019)
	Histone H1	IP, MS, UbA		(Liu et al., 2005; Mandemakers et al., 2017)
	Histone H2A	IP, MS, UbA		(Liu et al., 2005)
	Histone H2AX	IP, MS, UbA, WB		(Atsumi et al., 2015; Bose et al., 2017; Choe et al., 2016; Fok et al., 2017)
	Histone H2B	IP, MS, UbA		(Liu et al., 2005)
	Histone H3	IP, MS, UbA		(Liu et al., 2005)
	Histone H4	IP, MS, UbA		(Liu et al., 2005)
	Histone deacetylase 2 (HDAC2)	UbA, WB		(Zhang et al., 2011)
	Induced myeloid leukemia cell differentiation protein Mcl-1 (MCL1, BCL2L3)	FBA, IP, UbA, WB	BH3	(Kurokawa et al., 2013; Pandya et al., 2010; Thompson et al., 2014; Warr et al., 2005; Zhong et al., 2005)
	Leucine rich repeat scaffold protein SHOC-2 (SHOC2, KIAA0862)	2H, IP, UbA, WB	HECT	(Jang et al., 2014)
	Micro RNA-542-5p (miR-542-5p)	MS, WB		(Cheng et al., 2015)
	Mitofusin 2 (MFN2, CPRP1)	IP, MS, UbA		(Di Rita et al., 2018; Leboucher et al., 2012)

Mouse double minute 2 homolog (MDM2)	FBA, IP	1198-1205aa	(Kurokawa et al., 2013)	
Myc-interacting zinc finger protein 1 (MIZ1, ZBTB17)	IP, MS, UbA, WB		(Inoue et al., 2013; Peter et al., 2014; Yang et al., 2010)	
Myc proto-oncogene (C-myc, MYC, bHLHe39)	IP, UbA, WB		(Adhikary et al., 2005; Inoue et al., 2013; Peter et al., 2014; Qi et al., 2012)	
Myogenic determination protein 1 (MYOD1, BHLHC1, MYF3)	IP, MS, UbA, WB		(Noy et al., 2012)	
N-myc proto-oncogene protein (N-myc, MYCN, bHLHe37)	IP, MS, PD, UbA, WB		(King et al., 2016; Zhao et al., 2009b; Zhao et al., 2008)	
Peroxisome proliferator-activated receptor alpha (PPAR α , NR1C1)	IP, MS		(Zhao et al., 2018)	
Proliferating cell nuclear antigen (PCNA, Cyclin)	IF, IP, PD	PIP motif (3880-3887aa)	(Choe et al., 2016)	
Retinoblastoma binding protein 7 (RBBP7, RBAP46)	IP, PD, UbA, WB		(Liu et al., 2018)	
Serine/threonine Protein phosphatase 5 (PP5)	FBA, IP, UbA		(Kurokawa et al., 2013)	
T-lymphoma invasion and metastasis-inducing protein 1 (TIAM1)	IF, IP, WB		(Vaughan et al., 2015)	
Tumor suppressor alternative reading frame (ARF, p14 ^{ARF})	IP, MS, WB	1015-4574aa	(Chen et al., 2005; Qi et al., 2012)	
Ubiquitin thioesterase 7 (USP7, HAUSP)	IP, MS		(Thompson et al., 2014)	
Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA	HECT	(Chen et al., 2005; Cheng et al., 2016; Kristariyanto et al., 2015b; Schwarz et al., 1998)	
Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA		(Kristariyanto et al., 2015b)	
Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA		(Chen et al., 2005; Kristariyanto et al., 2015b)	
Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Kristariyanto et al., 2015b; Schwarz et al., 1998)	
Thyroid Receptor-Interacting Protein 12 (TRIP12, ULF, KIAA045) Gene: <i>TRIP12</i> Chromosome location: 2q36.3 Ub linkage types: K48, K63	Amyloid precursor protein-binding protein 1 (APP-BP1, NAE1)	2H, IP, UbA, WB	611-1259aa	(Park et al., 2008)
	Brg-1 associated factor 57 (BAF57, Smarce1)	IP, MS, PD, WB		(Keppler and Archer, 2010)
	Transcription factor SOX-6 (SOX6)	2H, IP, UbA, WB		(An et al., 2013)
	Tumor suppressor alternative reading frame (ARF, p14 ^{ARF})	IF, IP, MS		(Cai et al., 2015; Chen et al., 2010)
	Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	UbA	HECT	(An et al., 2013; Park et al., 2008; Schwarz et al., 1998)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA		(Schwarz et al., 1998)
	Ubiquitin thioesterase 7 (USP7, HAUSP)	IP, MS, UbA, WB	AWL	(Cai et al., 2015; Liu et al., 2016)
Ubiquitin-protein ligase E3B (UBE3B) Gene: <i>UBE3B</i> Chromosome location: 12q24.11 Ubiquitin Linkages: K48	Calmodulin (CaM)	IP, MS, UbA	IQ motif (29-58aa)	(Braganza et al., 2017)
Ubiquitin-protein ligase E3C (UBE3C, HECTH2, KIAA10, RAUL) Gene: <i>UBE3C</i> Chromosome location: 7q36.3 Ubiquitin Linkages: K11, K29 unanchored, K48	26S proteasome non-ATPase regulatory subunit 2 (PSMD2, RPN1, S2, p97)	PD	N-term (1-132aa)	(You and Pickart, 2001; You et al., 2003)
	26S proteasome non-ATPase regulatory subunit 6 (PSMD6, RPN7, S10)	IP		(You et al., 2003)
	26S proteasome regulatory subunit 8 (PSMC5, RPT6, S8, TRIP1)	IP		(You et al., 2003)
	Annexin A7 (ANXA7, Synixin)	IF, IP, MS, UbA		(Pan et al., 2015)
	Cullin-associated NEDD8-dissociated protein 2 (CAND2, TIP120B, KIAA0667)	IP, PD, UbA		(You et al., 2003)
	Estrogen receptor alpha (ER α)	IF, IP, MS, PD, SPR, UbA		(Okada et al., 2015)
	G2/mitotic-specific cyclin-B1 (CYB-1, CCNB1)	IP, MS, UbA		(Wang et al., 2013)
	Interferon regulatory factor 3 (IRF3)	IP, UbA		(Yu and Hayward, 2010)
	Interferon regulatory factor 7 (IRF7)	IP, UbA		(Yu and Hayward, 2010)
	Kaposi's sarcoma-associated herpesvirus immediate-early lytic cycle trigger protein RNA and transcription activator (KSHV RTA, HHV-8 RTA)	DeUbA, IP, UbA		(Yu and Hayward, 2010)
	Neuroblast differentiation-associated protein AHNAK (AHNAK, Desmoyokin)	IF, IP, MS, UbA		(Gu et al., 2019)
	Proteasomal ubiquitin receptor ADRM1 (hRPN13)	CE, MS, PD, UbA		(Besche et al., 2014; Kuo and Goldberg, 2017)
	Securin (IFY-1)	IP, MS, UbA		(Wang et al., 2013)
	Ubiquitin carboxyl-terminal hydrolase (Usp7, Deubiquitinase 7)	DeUbA, IP		(Yu and Hayward, 2010)

Ubiquitin-conjugating enzyme E2 D1 (UBE2D1, UBCH5A)	CE, CL, PD, UbA		(Besche et al., 2014; Byrne et al., 2017; Mastrandrea et al., 1999; Schwarz et al., 1998; You and Pickart, 2001; You et al., 2003; Yu and Hayward, 2010)
Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA, UbSu		(Byrne et al., 2017; Mulder et al., 2016)
Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA, MS		(Byrne et al., 2017; Huguenin-Dezot et al., 2016; Kristariyanta et al., 2015a; Okada et al., 2015)
Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA, UbSu, MS		(Byrne et al., 2017; Michel et al., 2015; Schwarz et al., 1998; Wang et al., 2013)
Ubiquitin pSer20	UbA		(Huguenin-Dezot et al., 2016)
Ubiquitin Protein Ligase E3			
Component N-Recognin 5 (UBR5, EDD, EDD1, HYD, DD5)	Adenomatous polyposis coli (APC)	IP, MS, IP, WB	(Ohshima et al., 2007)
Gene: UBR5	ATM interactor (ATMIN, ZNF822)	IP, MS, WB	(Wang et al., 2017; Zhang et al., 2014)
Chromosome location: 8q22.3	Beta-catenin (CTNNB1)	IF, IP, UbA, WB	(Flack et al., 2017; Hay-Koren et al., 2011)
Ub linkage types: K11, K29, K48	Bub3-interacting and GLEBS motif-containing protein ZNF207 (BuGZ, ZNF207)	IP, PD, WB	(Jiang et al., 2015)
	Centrosome and spindle pole-associated protein 1 (CSPP1)	IF, IP, PD, WB	(Shearer et al., 2018)
	Cyclin-dependent kinase 9 (CDK9, CDC2L4, TAK)	UbA	(Cojocaru et al., 2011)
	Cyclin-dependent kinase inhibitor 1 (CKI-1, p21, MDA-6)	2H, PD	(Ji et al., 2017)
	DNA topoisomerase II-β-binding protein 1 (TopBP1)	2H, IP, UbA, WB	(Honda et al., 2002)
	Dual specificity tyrosine-phosphorylation-regulated kinase 2 (DYRK2)	IP, PD	(Jung et al., 2013; Maddika and Chen, 2009)
	Esophageal cancer-related gene 4 (ECRG4, Augurin)	IP, WB	(Wang et al., 2017)
	Estrogen receptor alpha (ER-α, ESR1)	IF	(Bolt et al., 2015)
	FACT complex subunit SPT16 (SPT16, FACTp140)	IP, MS, WB	(Sanchez et al., 2016)
	FACT complex subunit SSRP1 (SSRP1, FACTp80)	IP, MS, WB	(Sanchez et al., 2016)
	Glycogen synthase kinase 3 beta (GSK-3β)	IF, IP, PD	(Hay-Koren et al., 2011)
	Histone acetyltransferase KAT5 (KAT5, TIP60)	IP, MS, WB	(Subbaiah et al., 2016)
	Human T-cell leukemia virus type-1 (HTLV-1) basic leucine zipper factor (HBZ)	IP, MS, PD, WB	(Panfil et al., 2018)
	Mitotic checkpoint protein BUB3 (BUB3)	IP, PD, WB	(Jiang et al., 2015)
	Modulator of apoptosis 1 (MOAP-1, MAP-1, PNMA4)	IP, UbA, WB	(Matsuura et al., 2017)
	OUT domain-containing protein 5 (OTUD5, DUBA)	IP, MS, PLA, WB	(de Vivo et al., 2019)
	p90 ribosomal S6 kinase (p90RSK, MAPKAPK-1a)	IP, WB	(Cho et al., 2017)
	Poly(A)-binding protein (PABP) interacting protein 2 (PAIP2)	IP, ITC, NMR, PD, UbA, WB	MLLE (Muñoz-Escobar et al., 2015; Yoshida et al., 2006)
	Phosphoenolpyruvate carboxykinase, cytosolic (PEPCK-C, PEPCK1)	IP, MS, PD, TAP	HECT N-lobe (Jiang et al., 2011; Shen et al., 2018)
	Polycomb group RING finger protein 4 (BMI1, RNF51)	IF, IP, MS, WB	(Sanchez et al., 2016)
	Transcription elongation factor S-II (TFIIS, TCEA2)	IP, MS, PD, TAP, WB	(Cojocaru et al., 2011)
	Transducin-like enhancer protein 3 (TLE3, ESG3)	IP, MS, UbA	(Flack et al., 2017)
	Trinucleotide repeat-containing gene 6A protein (TNRC6A, GW182)	NMR	MLLE (Muñoz-Escobar et al., 2015)
	Ubiquitin-conjugating enzyme E2 D2 (UBE2D2, UBCH5B)	UbA	HECT (Cojocaru et al., 2011; Honda et al., 2002; Jung et al., 2013; Matsuura et al., 2017; Matta-Camacho et al., 2012)
	Ubiquitin-conjugating enzyme E2 D3 (UBE2D3, UBCH5C)	UbA	HECT (Honda et al., 2002)
	Ubiquitin-conjugating enzyme E2 L3 (UBE2L3, UBCH7, UBCE7)	UbA	HECT (Flack et al., 2017; Honda et al., 2002)

Detection methods: **2H**, yeast or mammalian-two hybrid; **CE**, co-elution during chromatography purification; **CL**, chemical crosslinking; **DeUbA**, *in vivo* or *in vitro* deubiquitylation assay; **FBA**, *in vitro* filter binding assay; **FRET**, *in vivo* or *in vitro* fluorescence resonance energy transfer; **IF**, immunofluorescence; **IP**, immunoprecipitation; **ITC**, isothermal calorimetry; **MS**, liquid chromatography or MALDI MS/MS; **NMR**, nuclear magnetic resonance; **PD**, pulldown using GST, His or MBP tag; **PLA**, proximity ligation assay; **SPR**, surface plasmon resonance; **TAP**, tandem affinity purification; **UbA**, ubiquitylation assay; **UbSu**, ubiquitin suicide inhibition; **WB**, immunoblot.

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