

APPENDICES

Appendix A.1: Self activation and titration trial for β -catenin FAM binding region DBD. Self activation of a β -catenin FAM binding region (FBR)/Gal4 DNA binding domain fusion protein was assessed by growing yeast transformed with the expression construct for this fusion (pDest32 β -catenin FBR) on plates lacking in histidine and containing increasing concentrations of the histidine biosynthesis inhibitor 3AT. A master plate **F**) was used to replica plate transformed and control yeast strains onto test plates with 10 mM **A**), 25 mM **B**), 50 mM **C**), 75 mM **D**), or 100 mM **E**) 3AT. Growth of pDest32 β -catenin FBR transformed yeast was only seen at the 10 mM and very slightly at the 25 mM concentrations of 3AT. **G**) Diagram showing the arrangement of experimental and control yeast strains on master and test plates.

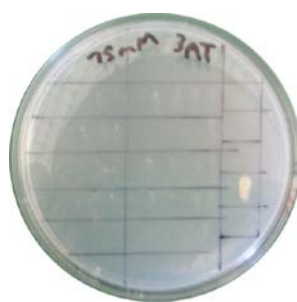
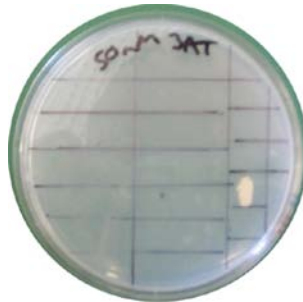
A) -His + 10mM 3AT

B) -His + 25mM 3AT



C) -His + 50mM 3AT

D) -His + 75mM 3AT



E) -His + 100mM 3AT

F) Master Plate



G)

pD32-FBR β-catenin/pD22 FLF	pD32-FBR β-catenin/ pD22 N1	Control A - None
pD32-FBR β-catenin/ pD22 EGFP	pD32-FBR β-catenin/ pD22 N2	Control B - Weak
pD32-FBR β-catenin/ pD22 ECT	pD32-FBR β-catenin/ pD22 C1	Control C - Moderate
pD32-FBR β-catenin/ pEXP AD	pD32-FBR β-catenin/ pD22 C2	Control D - Strong
	pD32-FBR β-catenin/ pD22 F.C.	Control E - Very Strong

Appendix A.2: Self activation and titration trial for E-cadherin cytoplasmic domain-DBD. Self activation of an E-cadherin cytoplasmic domain (ECT)/Gal4 DNA binding domain (DBD) fusion protein was assessed by growing yeast transformed with the expression construct for this fusion (pDest32 ECT) on plates lacking in histidine and containing increasing concentrations of the histidine biosynthesis inhibitor 3AT. A master plate **F**) was used to replica plate transformed and control yeast strains onto test plates with 10 mM **A**), 25 mM **B**), 50 mM **C**), 75 mM **D**), or 100 mM **E**) 3AT. Growth of pDest32 ECT transformed yeast was only seen at the 10 mM concentration of 3AT. **G**) Diagram showing the arrangement of experimental and control yeast strains on master and test plates.

A) -His + 10mM 3AT



B) -His + 25mM 3AT



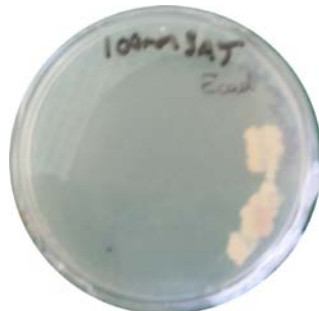
C) -His + 50mM 3AT



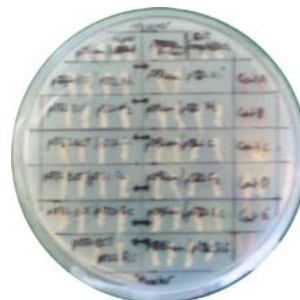
D) -His + 75mM 3AT



E) -His + 100mM 3AT



F) Master Plate



G)

pDBleu /		pEXPAD/ pD32-ECT	
pDBleu / pD22 N1		pD32-ECT/pD22 N1	Control A - None
pDBleu / pD22 N2		pD32-ECT/pD22 N2	Control B - Weak
pDBleu / pD22 C1		pD32-ECT/pD22 C1	Control C - Moderate
nDBleu / nD22 C2		pD32-ECT/pD22 C2	Control D - Strong
pDBleu / pD22 F.C.		pD32-ECT/pD22 F.C.	Control E - Very Strong
pDBleu / pD22 FLF		pD32-ECT/pD22 FLF	

Appendix A.3: Self activation and titration trial for *Epsin1-AD*. Self activation of an Epsin1/Gal4 activation domain (AD) fusion protein was assessed by growing yeast transformed with the expression construct for this fusion (pDest22 Epsin1) on plates lacking in histidine and containing increasing concentrations of the histidine biosynthesis inhibitor 3AT. Cells were replica plated onto test plates containing 10 mM **A**), 25 mM **B**), 50 mM **C**), 75 mM **D**), or 100 mM **E**) 3AT. Growth of pDest22 Epsin1 transformed yeast was only seen at the 10 mM, 25 mM, and 50 mM concentrations of 3AT. F) Diagram showing the arrangement of experimental and control yeast strains on the test plates.

A) -His + 10mM 3AT



B) -His + 25mM 3AT



C) -His + 50mM 3AT



D) -His + 75mM 3AT

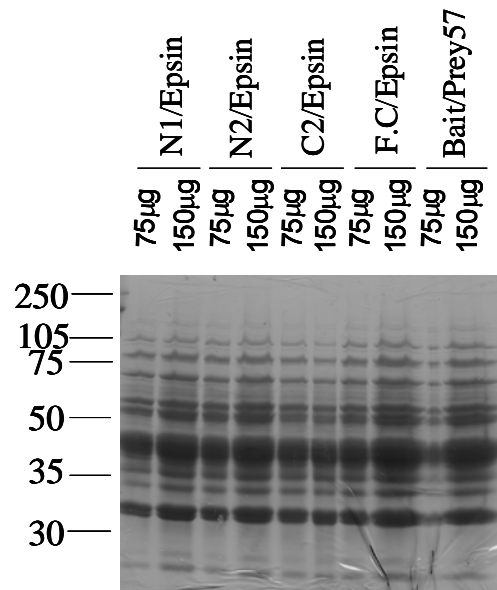


E) -His + 100mM 3AT



F)

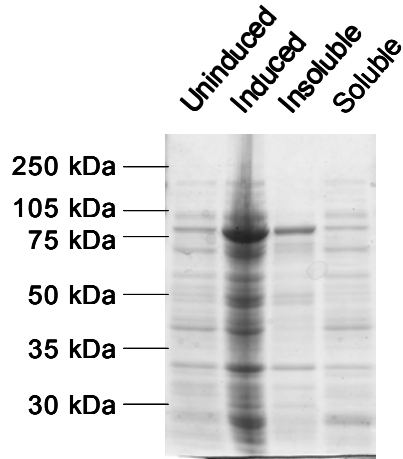
pD32-N!/pD22 Epsin1	
pD32-N2/pD22 Epsin1	Control A - None
pD32-C1/pD22 Epsin1	Control B - Weak
pD32-C2/pD22 Epsin1	Control C - Moderate
pD32-F.C./pD22 Epsin1	Control D - Strong
pD32-FLF/pD22 Epsin1	Control E - Very Strong
	Independent +ve Control



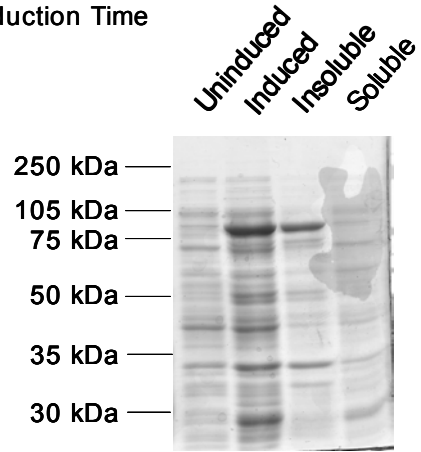
Appendix B: Coomassie blue stained gel of yeast cell extracts used in western analysis demonstrating that yeast proteins were successfully extracted from the cells.

Appendix C: Bacterial inductions of GST fusions of predicted FAM domains 2, 4, 5, 6, and 7 using modified expression protocol and alternative bacterial cell lines did not improve expression or solubility. A number of modifications were made to the standard bacterial expression protocol. Inductions were performed using a lower concentration of IPTG (0.05 mM) at 37°C **A**) and 25°C **C**) for FD2, and at 37°C **L**). Rosetta DE3 cells were used in place of BL21 cells to aid in the expression of fusion proteins whose cDNA contains codons that are rarely used in *E. Coli*. Inductions in Rosetta DE3 cells were performed at 25°C for FD4 **H**), FD5 **J**), and FD6 **Q**). Inductions in Rosetta DE3 cells were also performed at 37°C for FD4 **I**), FD5 **K**), and FD6 **R**). A shorter induction time coupled with a higher OD at the point of induction was trialed at 37°C **B**) and 25°C **D**) for FD2, and at 37°C **M**) for FD5. Two different lysis methods, heat lysis and sonication, were trialed for their effectiveness in extracting soluble expressed fusion proteins from bacterial cell pellets. Sonication was used to lyse cell pellets from cultures grown at 37°C for FD2 **E**) and FD7 **S**). Alternatively, heat lysis was used to lyse cell pellets from cultures also grown at 37°C for FD2 **F**) and FD7 **T**). Both lysis methods were also used at 25°C **N**) or 37°C **O**), to determine their effectiveness in extracting soluble expression fusion protein from Rosetta DE3 cells transformed with the GST fusion expression plasmid for FD5. To determine if expression of GST fusion protein before induction was a causative factor in the insolubility of expressed FD5 **P**), and FD7 **U**), glucose was added to the growth media to inhibit any leaky expression.

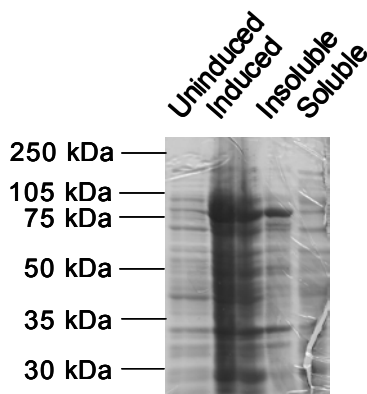
A) Fam Domain 2: BL21
37°C 0.05 mM IPTG



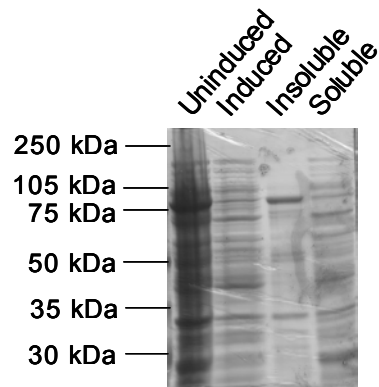
B) Fam Domain 2: BL21
37°C Greater OD Shorter
Induction Time



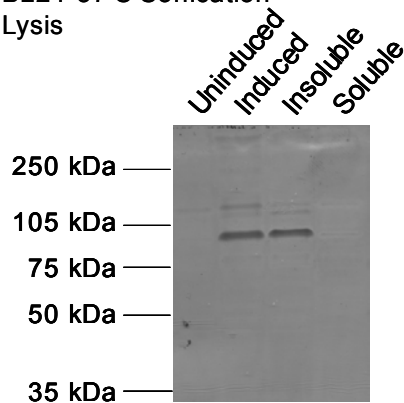
C) Fam Domain 2:
BL21 25°C Less IPTG



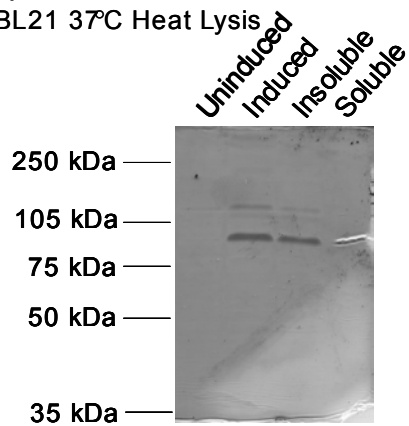
D) Fam Domain 2: BL21
37°C Greater OD Shorter
Induction Time



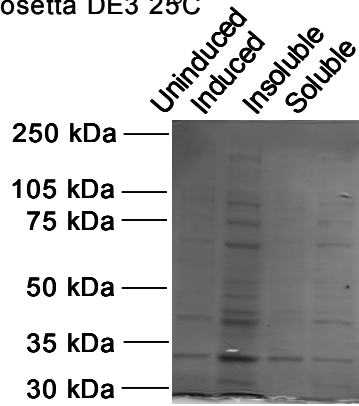
E) Fam Domain 2:
BL21 37°C Sonication
Lysis



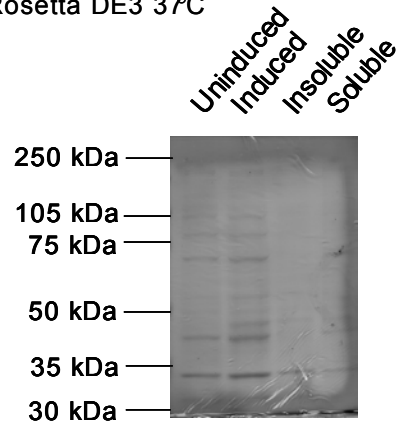
F) Fam Domain 2:
BL21 37°C Heat Lysis



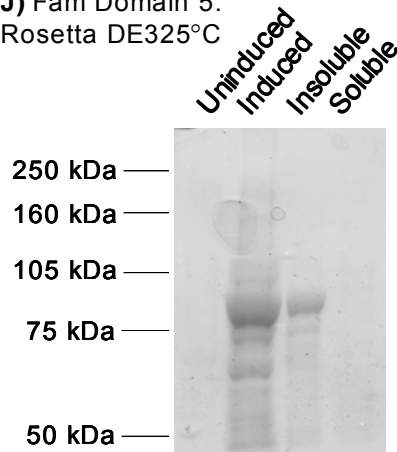
H) Fam Domain 4:
Rosetta DE3 25°C



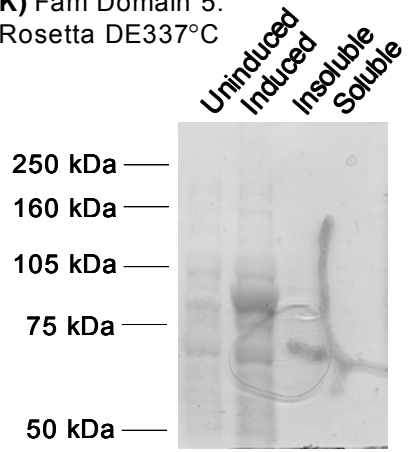
I) Fam Domain 4:
Rosetta DE3 37°C



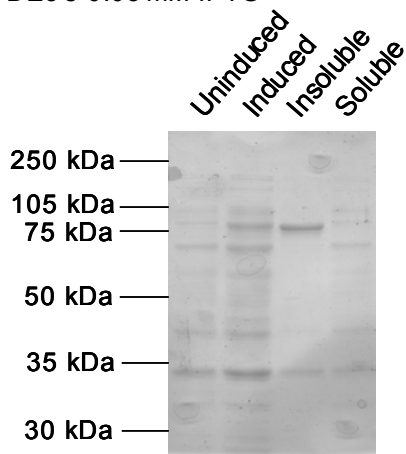
J) Fam Domain 5:
Rosetta DE3 25°C



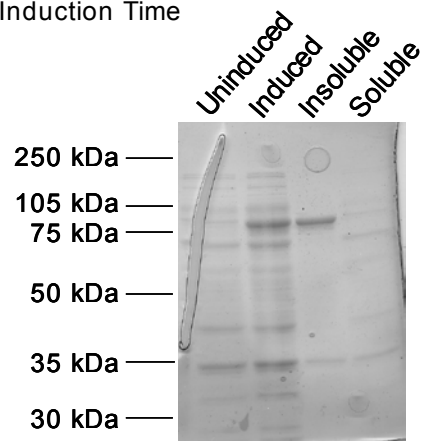
K) Fam Domain 5:
Rosetta DE3 37°C



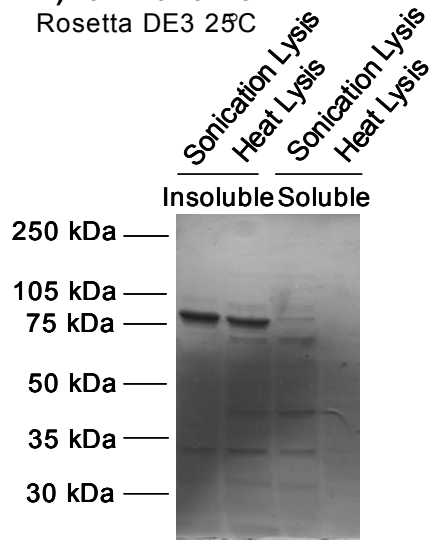
L) Fam Domain 5: Rosetta DE3's 0.05 mM IPTG



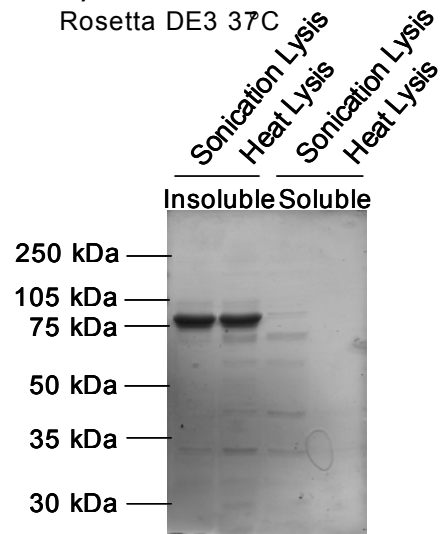
M) Fam Domain 5: Rosetta DE3's Greater OD Shorter Induction Time



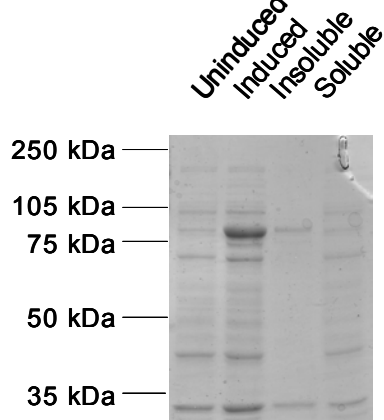
N) Fam Domain 5:
Rosetta DE3 25°C



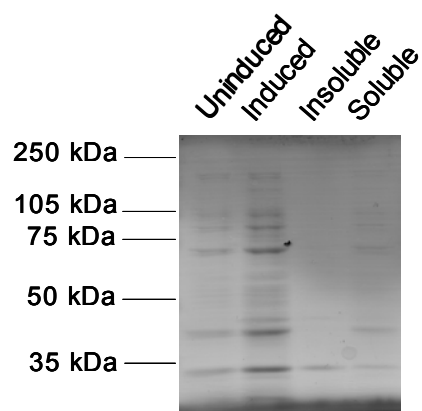
O) Fam Domain 5:
Rosetta DE3 37°C



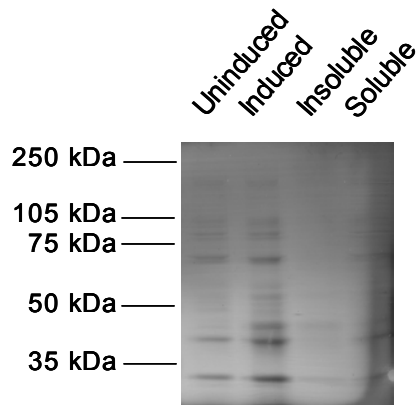
P) Fam Domain 5:
BL21 37°C + Glucose



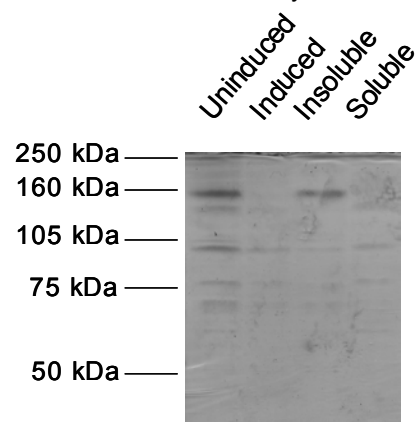
Q) Fam Domain 6: Rosetta
DE3 25°C



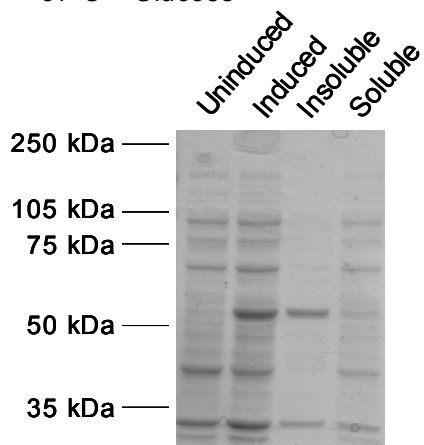
R) Fam Domain 6: Rosetta
DE3 37°C



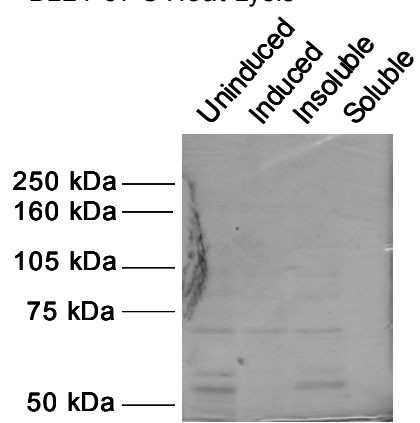
S) Fam Domain 7: BL21
37°C Sonication Lysis



U) Fam Domain 7: BL21
37°C + Glucose



T) Fam Domain 7:
BL21 37°C Heat Lysis



Appendix D: *FAM shares a high degree of sequence homology with its human Y-homologue.* A sequence alignment of the protein sequence of FAM with its human Y-homologue, USP9Y, shows that the two proteins are 90% identical.

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      10      20      30      40      50      60      70      80      90     100
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  MTAITHGSPVGGNDSQGQVLDGQSQHLFQQNQTSPPDSSNENSVATPPP EEQQGDAPPQHEDEEPAFPHTELANLDDMINRPRWVVPVLPKGELEVLLE
Consensus MTA T GSPVGGND QGQ  DGQSQ  QQNQTSPPDSSNENS ATPP  EQQGDAPPQ  EDEEPAFPHT LA LDDMINRPRWVVPVLPKGELEVLLE

      110     120     130     140     150     160     170     180     190     200
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  AAIDLSVKGKLDVKSEACQRFRRDGLTISFTKILMDEAVSGWKFEIHRCIINNTHRLVELCVAKLSQDWFPLLELLAMALNPHCKFHIYNGTRPCELISSN
Consensus AAIDLS KGLDVKSEACQRFRRDGLTISFTKIL DEAVSGWKFEIHRCIINNTHRLVELCVAKL QDWFPLLELLAMALNPHCKFHIYNGTRPCE  SS

      210     220     230     240     250     260     270     280     290     300
mUSP9X  VQLPEDELFARSPDPRSPKGWLVDLLNKFGLTNGFQILHDFRINGSALNVQIIAALIKPFGQCYEFLTLHTVKKYFLPIIEMVPQFLENLTDEELKKEAK
hUSP9Y  AQLPEEELFARSSDPRSPKGWLVDLINKFGLTNGFQILHDFRFFNGSALNIQIIAALIKPFGQCYEFLSQHTLKKYFIPVIEIVPHLLENLTDEELKKEAK
Consensus  QLPE ELFARS DPRSPKGWLVDL NKFGLTNGFQILHDFR NGSALN QIIAALIKPFGQCYEFL HT KKYF P IE VP LENLTDEELKKEAK

      310     320     330     340     350     360     370     380     390     400
mUSP9X  NEAKNDALSMIIKSLKNLASRVPGQEETVKNLEIFRLKMILRLLQISSFNGKMNALNEVKNVISSVSYTHRHGSSSEDEEWLTAERMAEWIQQNNILSIV
hUSP9Y  NEAKNDALSMIIKSLKNLASRISGQDETIKNLEIFRLKMILRLLQISSFNGKMNALNEINKVISSVSYTHRHSNPEEEEWLTAERMAEWIQQNNILSIV
Consensus NEAKNDALSMIIKSLKNLASR  GQ ET KNLEIFRLKMILRLLQISSFNGKMNALNE NKVISSVSYTHRH  E EEWLTAERMAEWIQQNNILSIV

      410     420     430     440     450     460     470     480     490     500
mUSP9X  LRDSLHQPYVEKLEKILRFVIKEKALTLDLNDNIWAAQAGKHEAIVKNVHDL LAKLAWDFSP EQLDHLDFCFKASWTNASKKQREKLELIRRLAEDDK
hUSP9Y  LQDSLHQPYVEKLEKILRFVIKEKALTLDLNDNIWAAQAGKHEAIVKNVHDL LAKLAWDFSPGQLDHLDFCFKASWTNASKKQREKLELIRRLAEDDK
Consensus L DSLHQPYVEKLEKILRFVIKEKALTLDLNDNIWAAQAGKHEAIVKNVHDL LAKLAWDFSP QLDHLDFCFKASWTNASKKQREKLELIRRLAEDDK

      510     520     530     540     550     560     570     580     590     600
mUSP9X  DGVMAHKVLNLLWNLAHSDDVPVDIMDLALSAHIKILDYSCSQDRDTQKIQWIDRFIEELRTNDKWVIPALKQIREICSLFGEAPQNLSQSQRSPHFVYR
hUSP9Y  DGVMAHKVLNLLWNLAQSDDVPVDIMDLALSAHIKILDYSCSQDRDAQKIQWIDHFIIEELRTNDKWVIPALKQIREICSLFGEASQNLSTQQRSPHFVYR
Consensus DGVMAHKVLNLLWNLA SDDVPVDIMDLALSAHIKILDYSCSQDRD QKIQWID FIEELRTNDKWVIPALKQIREICSLFGEA QNLSQ QRSPH FYR

      610     620     630     640     650     660     670     680     690     700
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
Consensus  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|

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Consensus SALQSIPNPSSEC LRN S LAQ IS EASRYMPDICVIRAI IIW S CG L L FSPNEE TKIY T G N EDEQVCCEALEVMTLCFAL

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 mUSP9X IPTALDALSKEKAWQTFIIDLLHCHSKTVRQVAQEQFFLMCTRCCMGHRPLLFFITILLFTVLGSTARERAKHSGDYFTLLRHLLNYAYNSNINVPNAEV
 hUSP9Y LPTALDALSKEKAWQTFIIDLLHCHSKTVRQLAQEQFFLMCTRCCMGHRPLLFFITILLFTVLGSTARERAKHSGDYFTLLRHLLNYAYNGNINIPNAEV
 Consensus PTALDALSKEKAWQTFIIDLLHCHSKTVRQ AQEQFFLMCTRCCMGHRPLLFFITILLFT LGSTARE K SGDYFTLLRHLLNYAYN NIN PNAEV

1410 1420 1430 1440 1450 1460 1470 1480 1490 1500
 mUSP9X LLNNEIDWLKRIRDVVKRTGETGVVEETILEGHLGVTKEKLLAFQTPEKKFHIGCEKGGANLIKELIDDFIFPASNVYLQYMRNGELPAEQAIIPVCGSPATI
 hUSP9Y LLVSEIDWLKRIRDVVKNTGETGVVEEPILEGHLGVTKEKLLAFQTSEKKYHFGCEKGGANLIKELIDDFIFPASKVYLQYLRSGELPAEQAIIPVCSPTI
 Consensus LL EIDWLKRIRD VK TGETGVVEE ILEGHLGVTKEKLLAFQT EKK H GCEKGGANLIKELIDDFIFPAS VYLQY R GELPAEQAIIPVC SP TI

1510 1520 1530 1540 1550 1560 1570 1580 1590 1600
 mUSP9X NAGFELLVALAVGCVRNKQIVDSLTEMYYIGTAITTCCEALTEWEYLPVGPVPPKGFVGLKNAGATCYMNSVIQQLYMIPSIIRNGILAIEGTGSVDVDD
 hUSP9Y NAGFELLVALAIGCVRNKQIVDCLTEMYYMGTAITTCCEALTEWEYLPVGPVPPKGFVGLKNAGATCYMNSVIQQLYMIPSIIRNSILAIEGTGSDDLHDD
 Consensus NAGFELLVALA GCVRNKQIVD LTEMYY GTAITTCCEALTEWEYLPVGPVPPKGFVGLKNAGATCYMNSVIQQLYMIPSIIRN ILAIEGTGS D DD

1610 1620 1630 1640 1650 1660 1670 1680 1690 1700
 mUSP9X MSGDEKQDNESNVDPRDDVFGYPQQFEDKPPLSKTEDRKEYNIGVLRHLQVIFGHLAASRLQYYVPRGFWKQFRLWGEVNLREQHDALEFFNSLVDSLD
 hUSP9Y MFGDEKQDNESNVDPRDDVFGYPHQFEDKPPALSKTEDRKEYNIGVLRHLQVIFGHLAASQLQYYVPRGFWKQFRLWGEVNLREQHDALEFFNSLVDSLD
 Consensus M GDEKQD ESNVDPRDDVFGYP QFEDKP LSKTEDRKEYNIGVLRHLQVIFGHLAAS LQYYVPRGFWKQFRLWGEVNLREQHDALEFFNSLVDSLD

1710 1720 1730 1740 1750 1760 1770 1780 1790 1800
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 hUSP9Y EALKALGHPAILSKVLGGSFADQKICQGCPRHFECEESFTTLNVDIRNHQNLDSLEQYIKGDLLEGANAYHCEKCDKKVDTVKRLLIKKLPVLAIQLK
 Consensus EALKALGHPA LSKVLGGSFADQKICQGCPRH ECEESFTTLNVDIRNHQNLDSLEQY KGDLLLEGANAYHCEKC KKVDTVKRLLIKKLP VLAIQLK

1810 1820 1830 1840 1850 1860 1870 1880 1890 1900
 mUSP9X RFDYDWERECAIKFNDFEFPRELDMPTVAVGVAKLEGDVNPESQLIQNEQSESEKAGSTKYRLVGVLVHSGQASGGHYYSYIIQRNGGDGKNRWY
 hUSP9Y RFDYDWERECAIKFNDFEFPRELDMPTVAVGANLERNVNSENELIEQKEQSDNETAGGTYRLVGVLVHSGQASGGHYYSYIIQRNGKDDQTDHWY
 Consensus RFDYDWERECAIKFNDFEFPRELDM PTVAVGVA LE DNVN E LI Q EQS E AG TKYRLVGVLVHSGQASGGHYYSYIIQRNG D WY

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      1910      1920      1930      1940      1950      1960      1970      1980      1990      2000
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  KFDDGDVTECKMDDDEEMKNQCFGGEYMGFVLDHMMKRMSYRRQKRWWNAYILFYERMDTIGHDDEVIRYISEIAITTRPHQIVMPSAIERSVRKQNVQF
Consensus KFDDGDVTECKMDDDEEMKNQCFGGEYMGFVLDHMMKRMSYRRQKRWWNAYI FYE MD I DDE IRYISE I PHQI M AIERSVRKQNV F

      2010      2020      2030      2040      2050      2060      2070      2080      2090      2100
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  MHNRMQYSLEYFQFMKLLTCNGVYLNPPPGQDHLSPFAEEITMISIQLAARFLFTTGFBTKKIVRGSASDWYDALCILLRHSKNVRFWFHNVLFNVSN
Consensus MHNRLQYSLEYFQFVKLLTCNGVYLNPA PGQDYLLPEAAEITMISIQLAARFLFTTGFBTKKIVRGPASDWYDALCVLLRHSKNVRFWFHNVLFNVSN

      2110      2120      2130      2140      2150      2160      2170      2180      2190      2200
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hUSP9Y  RFSEYLLECPFAEVRGAFKLVFIAHFSLQDGPSPFPASPGPSSQAYDNLSLSDHLLRAVLNLLRREVSEHGRHLQOYFNLFVMYANLGVAEKTQLLK
Consensus RFSEYLLECPFAEVRGAFKLVFIAHFSLQDGPSPFPASPGPSSQA DNLSLSDHLLRA LNLLRREVSEHG HLQOYFNLFVMYANLGVAEKTQLLK

      2210      2220      2230      2240      2250      2260      2270      2280      2290      2300
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hUSP9Y  LSVPATFMLVSLDEGPGPPIKYQYAEELGKLYSVVSQLIRCCNVSSRMQSSINGNPPLPNPFGDNLNSQPIMPIQQNVLDILFVRTSYVKKIIEDCSNSDE
Consensus L VPATFMLVSLDEGPGPPIKYQYAEELGKLYSVVSQLIRCCNVSS MQSSINGNP LPNPFGD NLSQPIMPIQQNV DILFVRTSYVKKIIEDCSNS

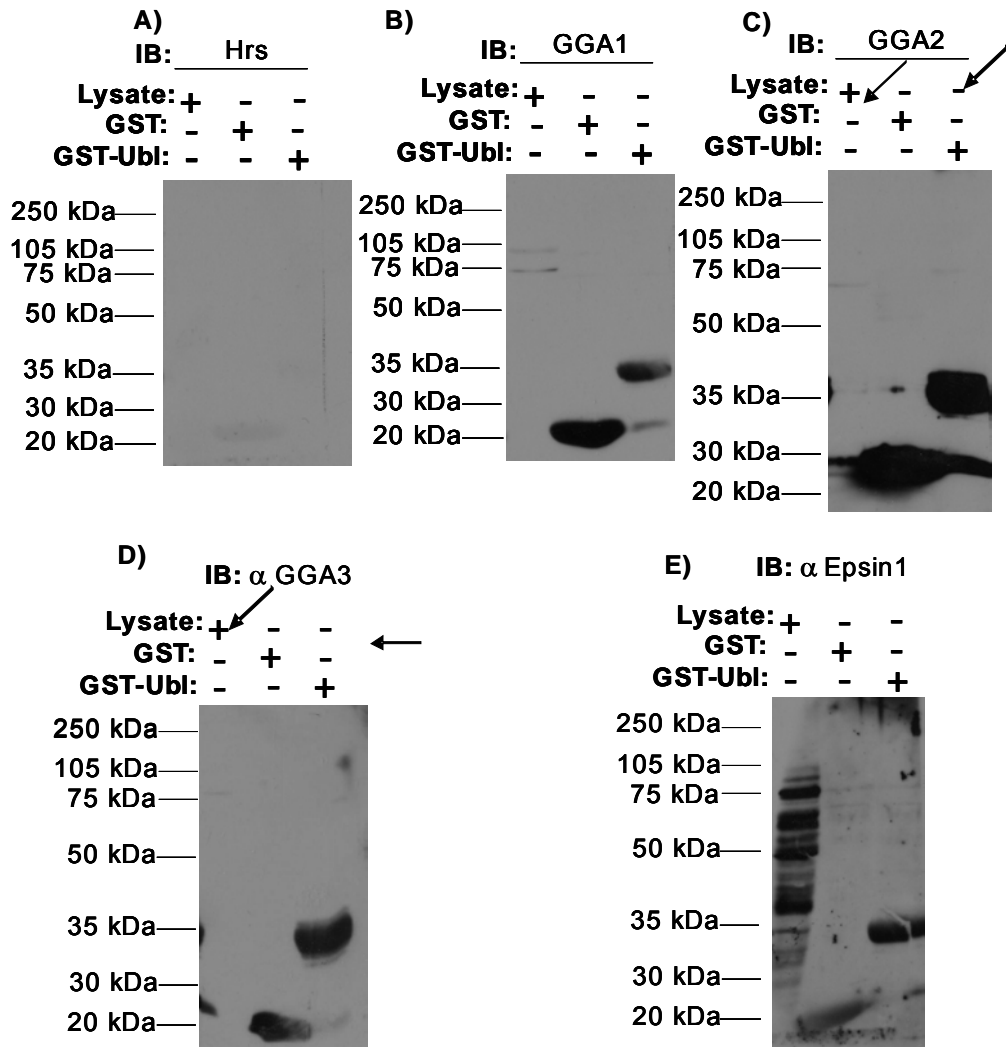
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hUSP9Y  TVKLLRFCCWENPQFSSTVLSSELLWQVAYSITYELRYPYLDLLQILLIEDSWQTHRIHNALKGIPDDRDLGFDFTIQRSKNHYQKRAYQCIKCMVALFSSC
Consensus T KLLRFCC WENPQFSSTVLSSELLWQVAYSITYELRYPYLDLL QILLIEDSWQTHRIHNALKGIPDDRDLGFDFTIQRSKNHYQKRAYQCIKCMVALFSSC

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mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  PVAYQILQGNGLKRWKWTWAVEWLGDELEERRPYTGNPQYTYNNWSPPVQSNETSNGYFLERSHSARMTLAKACELCPEEPPDDQDAPDEHESPPPEDAPL
Consensus PVAYQILQGNGLKRWKWTWAVEWLGDELEERRPYTGNPQY YNNWSPPVQSNETS NGYFLERSHSARMTLAKACELCPEEPPDDQDAPDEHE P EDAPL

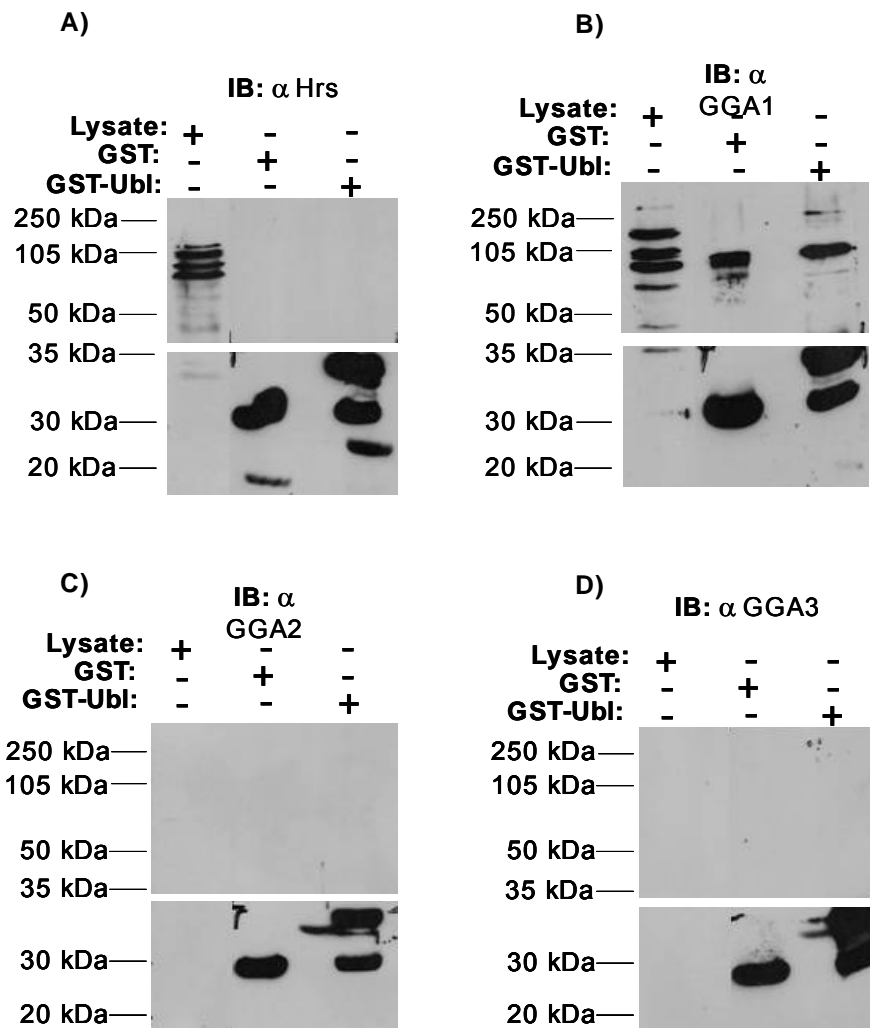
      2510      2520      2530      2540      2550
mUSP9X  ....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|....|
hUSP9Y  PVAYQILQGNGLKRWKWTWAVEWLGDELEERRPYTGNPQY YNNWSPPVQSNETS NGYFLERSHSARMTLAKACELCPEEPPDDQDAPDEHE P EDAPL
Consensus PVAYQILQGNGLKRWKWTWAVEWLGDELEERRPYTGNPQY YNNWSPPVQSNETS NGYFLERSHSARMTLAKACELCPEEPPDDQDAPDEHE P EDAPL

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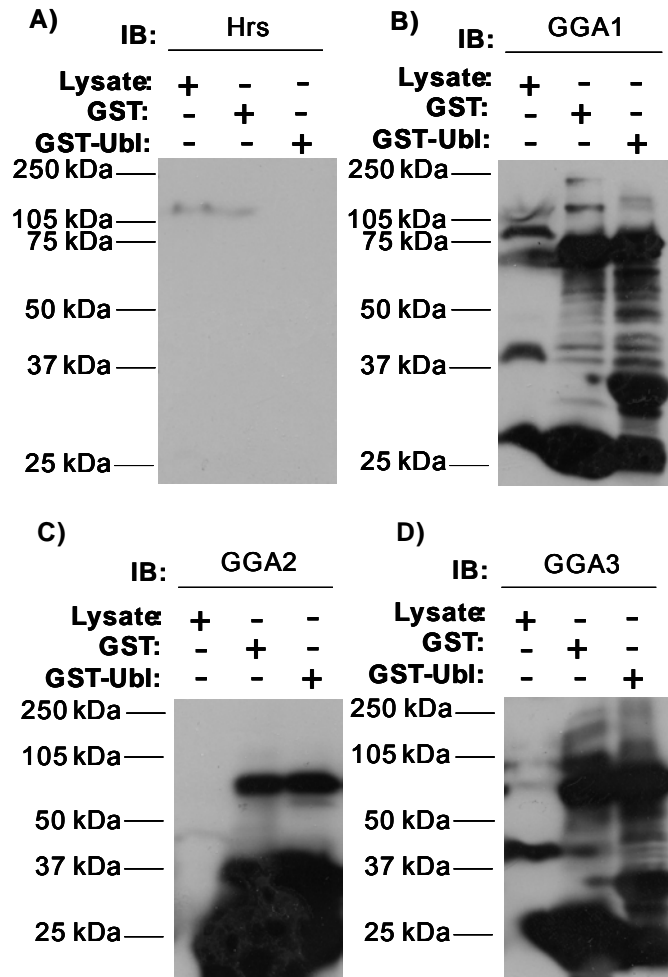
mUSP9X YPHSPGSQYQQNNHVGQPYTGPAAHHMNNPQRTGQRAQENYEGGEEVSPPQTKDQZ
hUSP9Y YPHSPASQYQQNNHVGQPYTGPAAHHLNNPQKTGQRTQENYEGNEEVSSPQMKDQ-
Consensus YPHSP SQYQQNNHVGQPYTGPAAHH NNPQ TGQR QENYEG EEVS PQ KDQ



Appendix E.1: GST-Pulldown – Best candidate approach attempt II. Affinity binding assays were carried out as previously described. Blots were cut into strips and probed with **A)** α Hrs, **B)** α GGA1, **C)** α GGA2, **D)** α GGA3, or **E)** α Epsin 1.



Appendix E.2: GST-Pulldown – Best candidate approach attempt III Affinity binding assays were carried out as previously described except that whole mouse brain cell lysate was used in place of HEK 293T cell lysate. Blots were cut into strips and probed with **A)** α Hrs, **B)** α GGA1, **C)** α GGA2, or **D)** α GGA3



Appendix E.3: GST-pulldown – Best candidate approach attempt IV Affinity binding assays were carried out as previously described except that total HeLa cell lysate was used in place of HEK 293T cell lysate. Blots were cut into strips and probed with **A)** α Hrs, **B)** α GGA1, **C)** α GGA2, or **D)** α GGA.

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