

## Supplementary Material

# ***Liaisons dangereuses: Intrinsic Disorder in Cellular Proteins Recruited to Viral Infection-Related Biocondensates***

Greta Bianchi <sup>1</sup>, Stefania Brocca <sup>1,\*</sup>, Sonia Longhi <sup>2,\*</sup> and Vladimir N. Uversky <sup>3</sup>


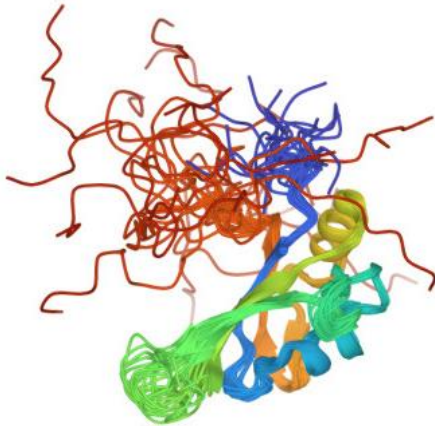
<sup>1</sup> Department of Biotechnology and Biosciences, University of Milano-Bicocca, 20126 Milano, Italy;  
g.bianchi31@campus.unimib.it


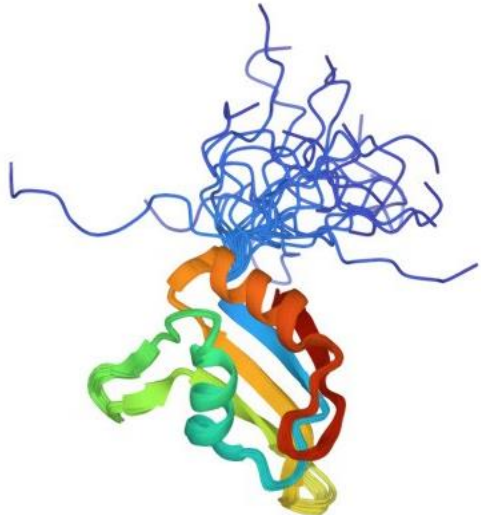
<sup>2</sup> Laboratoire Architecture et Fonction des Macromolécules Biologiques (AFMB), UMR 7257, Aix Marseille University and CNRS,  
13288 Marseille, France


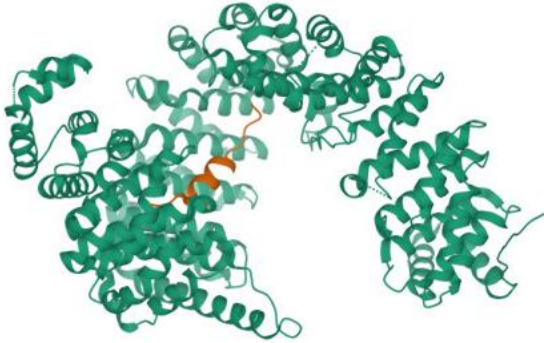
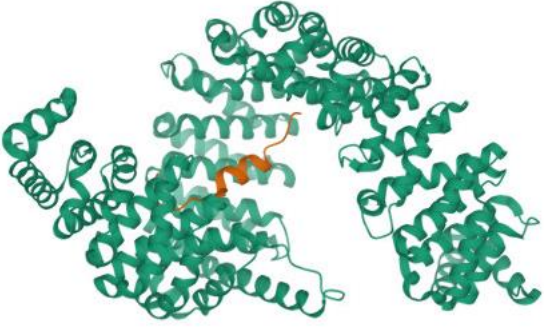
<sup>3</sup> Department of Molecular Medicine, Byrd Alzheimer's Research Institute, Morsani College of Medicine, University of South Florida,  
Tampa, FL 33601, USA; vuversky@usf.edu

\* Correspondence: stefania.brocca@unimib.it (S.B.); sonia.longhi@univ-amu.fr (S.L.)

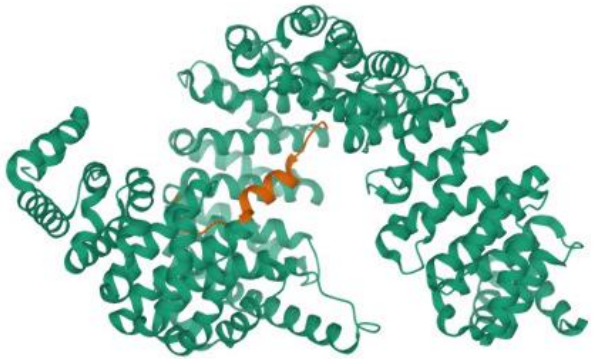
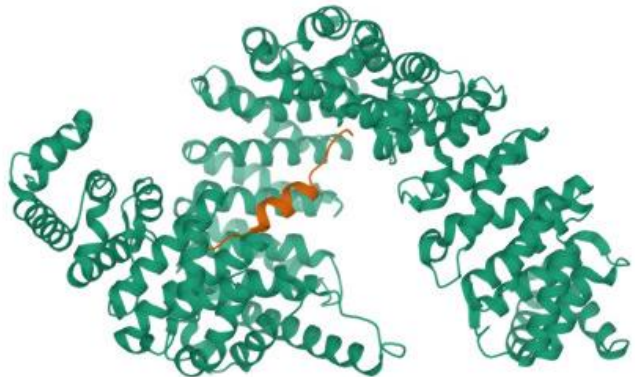
**Supplementary Table S1.** Structural information about proteins analyzed in this study

RNA-binding protein FUS (23 PDB entries; 526 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
6SNJ	NMR		A	260-390		PubMed: 33311468 Note: Complex of Complex of the FUS/TLS RNA recognition motif (green) with U1 snRNA stem loop III (orange)
2LCW	NMR		A	278-385		PDB DOI: 10.2210/pdb2LCW/pdb Note: solution structure of the FUS/TLS RRM domain

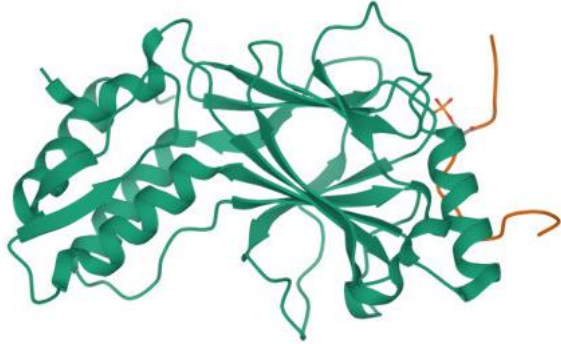

6GBM	NMR		B	280-377		<p>PubMed: 30581145</p> <p>Note: Complex of an RRM domain of FUS (green) with RNA (orange)</p>
2LA6	NMR		A	282-370		<p>PDB DOI: 10.2210/pdb2LA6/pdb</p> <p>Note: Solution structure of RRM domain of RNA-binding protein FUS</p>

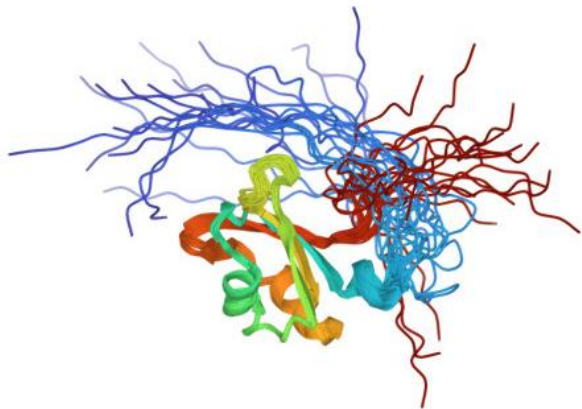
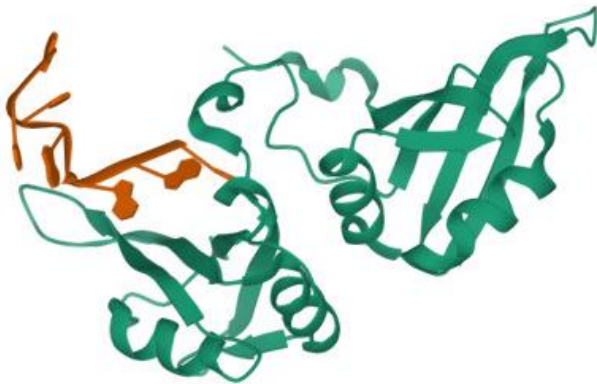
6G99	NMR		B	419-454		PubMed: 30581145 Note: Complex of a zinc-finger domain of FUS (green) with RNA (UGGUG; orange)
5YVG	X-ray	4.05	X/Y	1-526		PubMed: 29677513 Note: Complex of Transportin-1 also known as karyopherin-β2 (green) with full length FUS (orange). Only residues 517-523 are resolved; remaining part of FUS are not modeled (missing electron density region)
7CYL	X-ray	2.70 Å	B	476-526		PubMed: 33580145 Note: Complex of Transportin-1 also known as karyopherin-β2 karyopherin-β2 (green) with full length FUS (orange). Only residues 513-521 are resolved; remaining parts of FUS are not modeled (missing electron density regions)

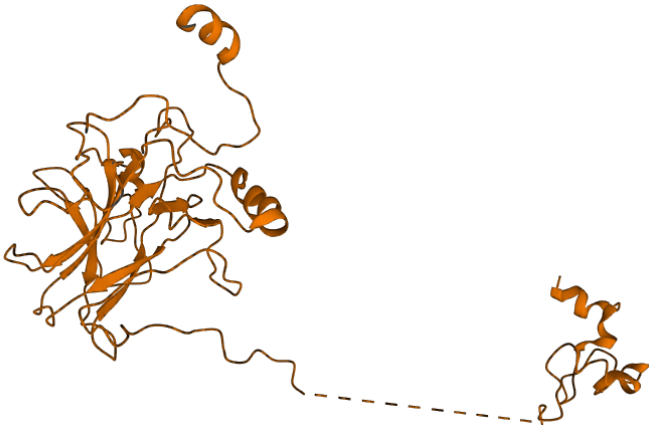
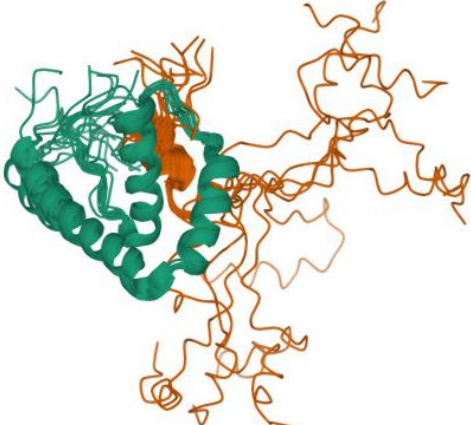



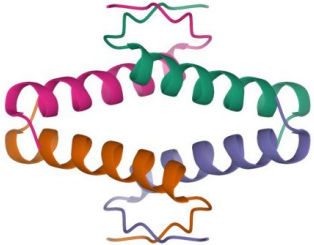
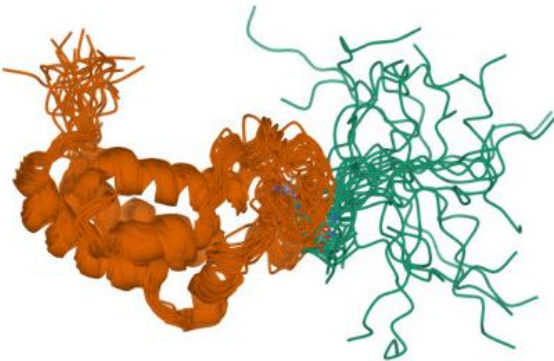
4FDD	X-ray	2.30 Å	B	498-526		<p>PubMed: 22778397</p> <p>Note: Complex of Transportin-1 also known as karyopherin-β2 (green) with a FUS fragment (orange); Only residues 513-522 are resolved; remaining parts of this FUS fragment are not modeled (missing electron density regions)</p>
4FQ3	X-ray	3.00 Å	B	495-526		<p>PDB DOI: 10.2210/pdb4FQ3/pdb</p> <p>Note: Complex of Transportin-1 also known as karyopherin-β2 (green) with a FUS fragment (orange); Only residues 513-522 are resolved; remaining parts of this FUS fragment are not modeled (missing electron density regions)</p>



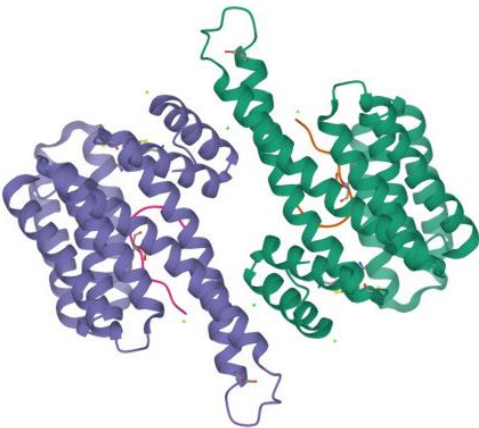
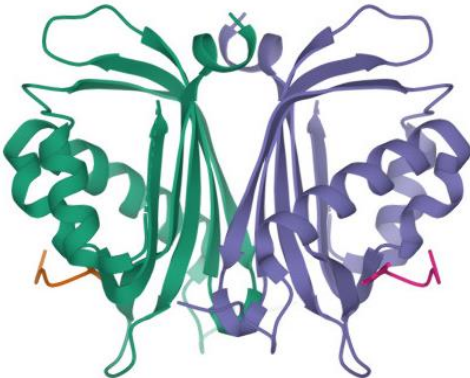
5JEK		2.40 Å	C/D	433-448		PubMed: 27302953 Note: Phosphorylated MAVS (orange) in complex with IRF-3 (green)
4Z8M	X-ray	2.95 Å	C/D	450-468		PubMed: 26385923 Note: A complex of MAVS (orange) with TRAF6 (green)

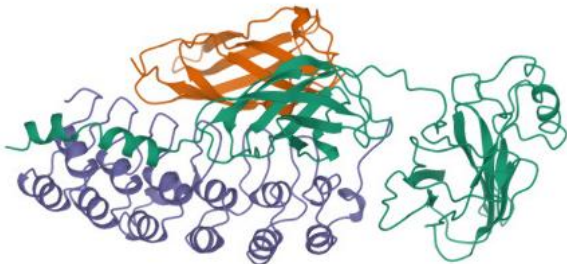

Heterogeneous nuclear ribonucleoprotein A2/B1 (hnRNP A2B1; 9 PDB entries; 353 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
1X4B	NMR		A	1-103		PDB DOI: 10.2210/pdb1X4B/pdb Note: Solution structure of RRM domain of hnRNP A2
5EN1	X-ray	2.58 Å	A	12-195		PDB DOI: 10.2210/pdb5EN1/pdb Note: Crystal structure of hnRNP A2B1 (green) in complex with RNA (orange)

Cellular tumor antigen p53 (TP53; 246 PDB entries; 393 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
6XRE	Cryo-EM	4.60 Å	M	1-393		PubMed: 33767390 Note: Structure of p53 is computationally extracted from the p53/RNA polymerase II assembly, which includes DNA-directed RNA polymerase II subunits RPB1, RPB2, RPB3, RPB4, RPB5, RPABC2, RPB7, RPABC3, RPB9, RPABC5, RPB11-a, RPABC4, and p53
2LY4	NMR		A	1-93		PubMed: 23063560 Note: Solution structure of a complex between high mobility group protein B1 (green) and a p53 transactivation domain (orange)

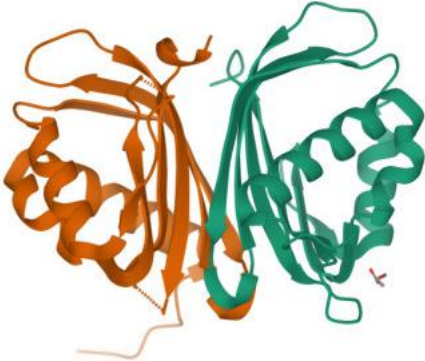

2MEJ	NMR			96-312		PubMed: 24814347 Note: Solution structure of a complex between BCL-xL (green) and the p53 core (DNA-binding) domain (orange)
1AIE	X-ray	1.50 Å	A	326-356		PubMed: 9761820 Note: Crystal structure of the homo-tetramer of the p53 tetramerization domain
1JSP	NMR		A	367-386		PubMed: 14759370 Note: solution structure of the Bromodomain of CREB-binding protein (orange) in a complex with the C-terminal negative regulatory domain of p53 (green)

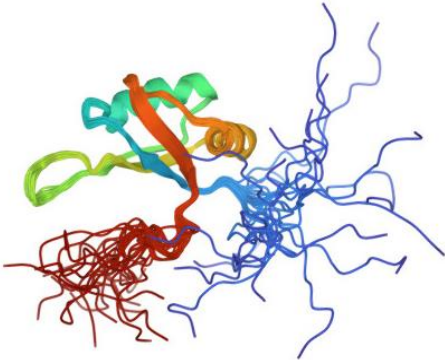
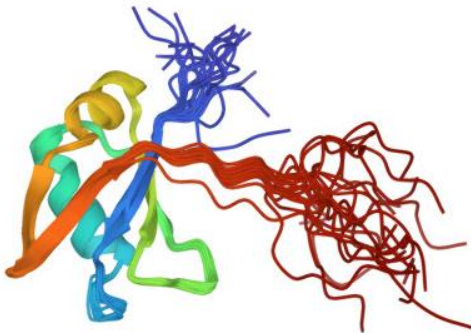
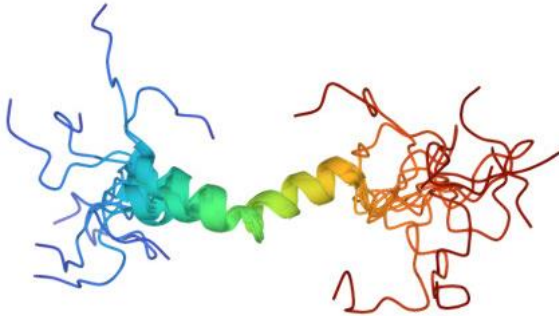


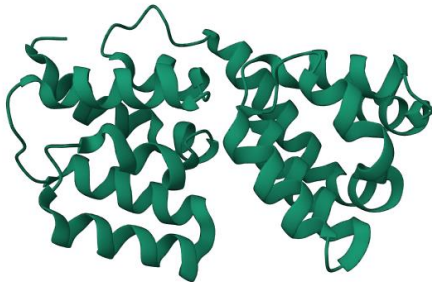
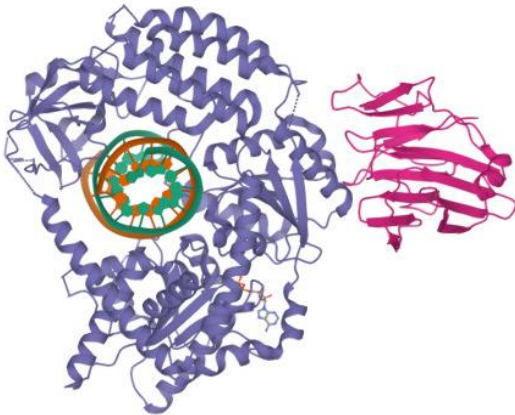
6R5L	X-ray	1.88 Å	P	385-393		PubMed: 32501690 Note: Crystal structure of a 14-3-3 sigma dimer (green and blue) with a C-terminal phosphorylated fragment of p53 (p53pT387, orange)
<b>Ras GTPase-activating protein-binding protein 2 (G3BP2; 1 PDB entry; 482 residues)</b>						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
5DRV	X-ray	2.75 Å	A	1-139		PubMed: 26410532 Note: A crystal structure of the G3BP2 NTF2-like domain (green and blue) in complex with a canonical FGDF motif peptide (orange and red)


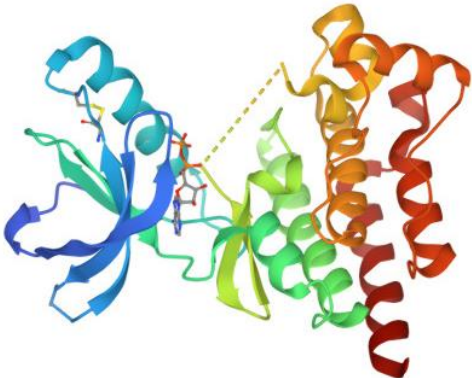
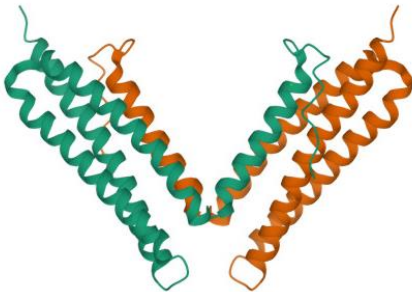
Transcription factor p65 (Nuclear factor NF-kappa-B p65 subunit; 88 PDB entries; 551 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
1NFI	X-ray	2.70 Å	A/C	20-320		PubMed: 9865693 Note: A crystal structure of the NF-kappa-B p65 (green) – NF-kappa-B p50 (orange) – I - kappa-B-alpha (blue) complex.
5U4K	NMR		B	521-551		PubMed: 28334776 Note: NMR structure of the complex between the KIX domain of CBP (green) and the transactivation domain 1 of p65 (orange)
Ras GTPase-activating protein-binding protein 1 (G3BP1; 7 PDB entries; 466 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference

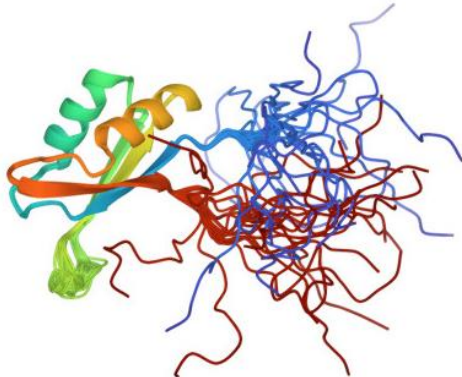
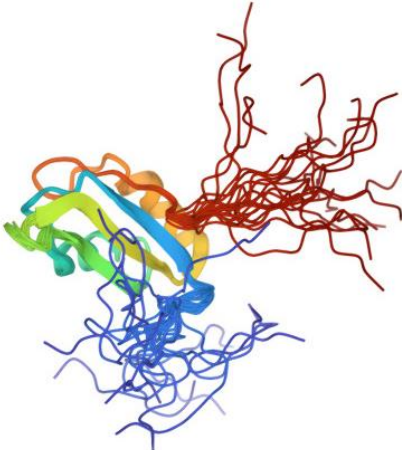
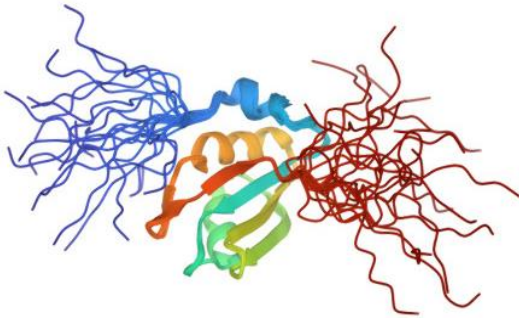


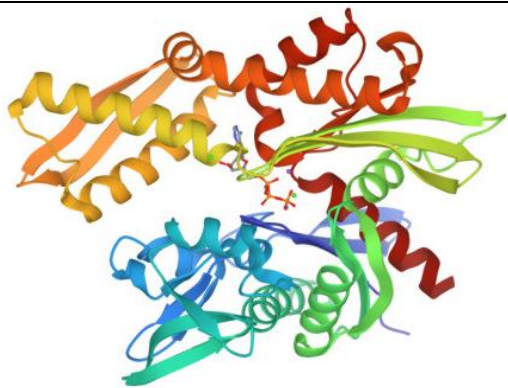
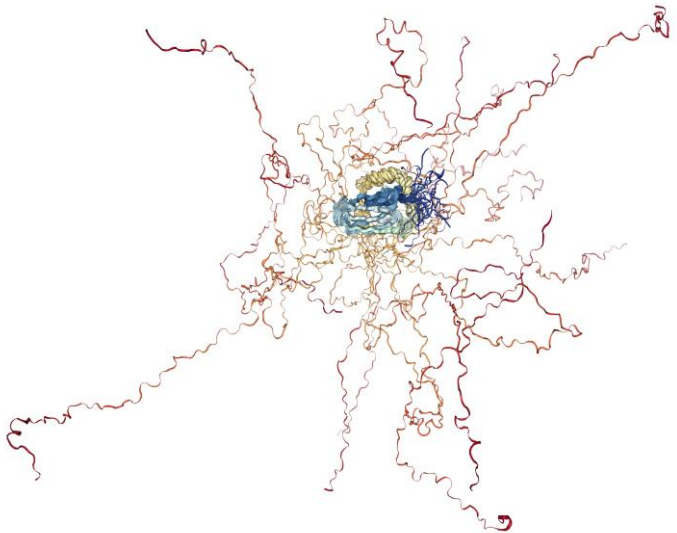
4FCJ	X-ray	1.62 Å	A/B	1-139		PubMed: 24324649 Note: Crystal homodimeric structure of the NTF2-like domain of human G3BP1
<b>TAR DNA-binding protein 43 (TDP-43; 34 PDB entries; 414 residues)</b>						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
2N4P	NMR		A	1-77		PubMed: 26756435 Note: Solution structure of the N-terminal domain of TDP-43

2CQG	NMR		A	96-185		PDB DOI: 10.2210/pdb2CQG/pdb Note: Solution structure of the RNA binding domain of TAR DNA-binding protein-43
1WF0	NMR		A	193-267		PDB DOI: 10.2210/pdb1WF0/pdb Note: Solution structure of RRM domain in TAR DNA-binding protein-43
2N3X	NMR		A	311-360		Note: Solution structure of TDP-43 amyloidogenic core region
<b>Nuclear transport factor 2 (NTF2) family protein with RNA binding (RRM-RBD-RNP motifs) domain-containing protein (no experimental structure; 458 residues)</b>						
<b>Melanoma differentiation-associated protein 5 (MDA-5; 8 PDB entries; 1,025 residues)</b>						
PDB ID	Method	Resolution	Chain	Position	Image	Reference

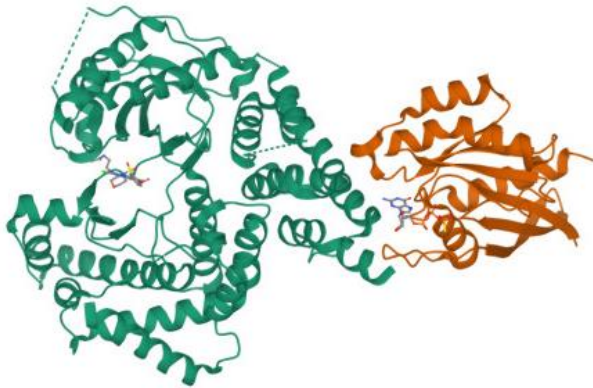

7DNJ	Cryo-EM	3.30 Å	A/B/C/D	1-208		PubMed: 34644557 Note: Structure is computationally extracted from K63-polyUb MDA5CARDs complex containing 4 MDA- chains and 8 ubiquitin chains
7JL0	Cryo-EM	4.30 Å	A	287-1025		PubMed: 33373584 Cryo-EM structure of MDA5 (blue) - dsRNA (green and orange) in complex with TRIM65 PSpy domain (pink)
<b>Fibrillarin 2 (no experimental structure; 314 residues)</b>						
<b>Focal adhesion kinase 1 (FAK1; 35 PDB entries; 1,052 residues)</b>						
PDB ID	Method	Resolution	Chain	Position	Image	Reference

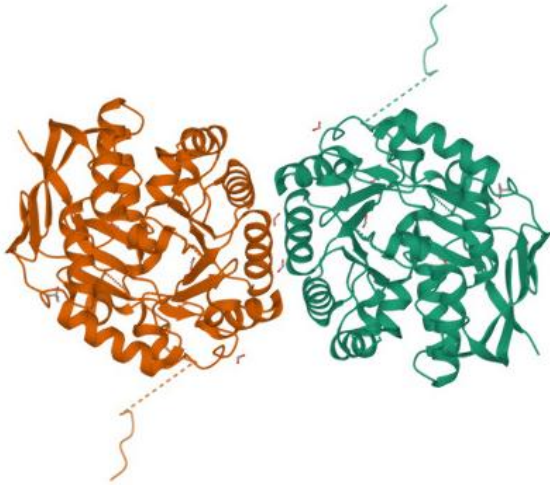

4NY0	X-ray	2.80 Å	A/B/C/D	31-405		PubMed: 24480479 Note: Crystal structure of FERM domain of human focal adhesion kinase
1MP8	X-ray	2.80 Å	A	406-686		PubMed: 12467573 Note: Structure contains 3 regions with missing electron density: residues 406-413, 445-446, and 565-583
1K04	X-ray	1.95 Å	A	891-1052		PubMed: 12005431 Note: Crystal structure of the focal adhesion targeting domain of focal adhesion kinase
<b>Nucleolysin TIAR (TIAR1; 3 PDB entries; 375 residues)</b>						
PDB ID	Method	Resolution	Chain	Position	Image	Reference

2CQI	NMR		A	1-90		PDB DOI: 10.2210/pdb2CQI/pdb Note: Solution structure of the RNA binding domain of Nucleolysin TIAR
2DH7	NMR		A	89-180		PDB DOI: 10.2210/pdb2DH7/pdb Note: Solution structure of the second RNA binding domain in Nucleolysin TIAR
1X4G	NMR		A	187-282		PDB DOI: 10.2210/pdb1X4G/pdb Solution structure of RRM domain in Nucleolysin TIAR

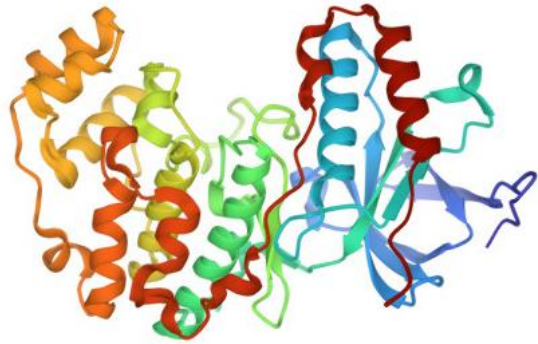
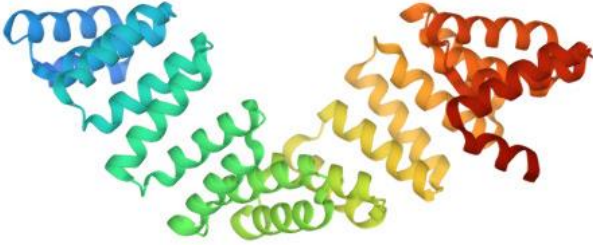
Heat shock 70 kDa protein 1A (HSP70-1A; 44 PDB entries; 641 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
1S3X	X-ray	1.84 Å	A	1-382		PubMed: 9083109 Note: The crystal structure of the human Hsp70 ATPase domain (or Nucleotide-binding domain (NBD))
5GJJ	NMR		A	385-641		PDB DOI: 10.2210/pdb5GJJ/pdb Note: Solution structure of substrate-binding domain (SBD)




Ras-related protein Rab-11A (RAB11; 28 PDB entries; 216 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
5FBL	X-ray	3.37 Å	B	1-216		PDB DOI: 10.2210/pdb5FBL/pdb Note: Crystal structure of a complex between Phosphatidylinositol 4-kinase beta (green) and RAB11 (orange); in RAB11 structure, residues 108, 68-73, and 177-216 are regions of missing electron density
Serine/threonine-protein phosphatase PP1-alpha catalytic subunit (PP1; 36 PDB entries; 330 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
3EGG	X-ray	1.85 Å	A/B	7-330		PubMed: 20305656 Note: Crystal structure of a complex between Protein Phosphatase 1 alpha (PP1; green) and the PP1 binding and PDZ domains of Spinophilin (orange); in PP1 structure, residues 301-330 represent a region of missing electron density

Glutamine-dependent carbamoyl-phosphate synthase (CAD; 34 PDB entries; 2,225 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
4C6B	X-ray	1.66 Å	A	1454-1846		PubMed: 24332717 Note: Crystal structure of the dihydroorotase domain of human CAD; residues 1454-1459, 1476-1482, 1650-1657, 1697-1698, 1824-1830, and 1840-1846 are missing
5G1N	X-ray	2.10 Å	A/B/C/D/E/F	1912-2225		PubMed: 27265852 Note: Crystal structure of the aspartate transcarbamoylase domain of human CAD; residues 1912-1919 are missing



Mitogen-activated protein kinase 14 (MAPK14; 245 PDB entries; 360 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
2LGC	NMR		A	2-354		PubMed: 22275118 Note: NMR solutions structure of MAPK14
UDP-N-acetylglucosamine--peptide N-acetylglucosaminyltransferase 110 kDa subunit or O-linked N-acetylglucosamine transferase 110 kDa subunit (OGT; 38 PDB entries; 1,046 residues)						
PDB ID	Method	Resolution	Chain	Position	Image	Reference
6EOU	X-ray	1.75 Å	A	23-410		PubMed: 29606577 Note: Crystal structure of the TPR domain of O-linked β-N-acetyl- D -glucosamine (O-GlcNAc) transferase (OGT); residues 23-57 and 401-410 represent regions of missing electron density

6IBO	X-ray	2.17 Å	A	319-1041		<p>PubMed: 31296563</p> <p>Note: Cristal structure of the catalytic OGT domain; residues 319-324, 726-728, 757-771, and 1038-1041 form regions of missing electron density</p>
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## Supplementary Figures S1–S18

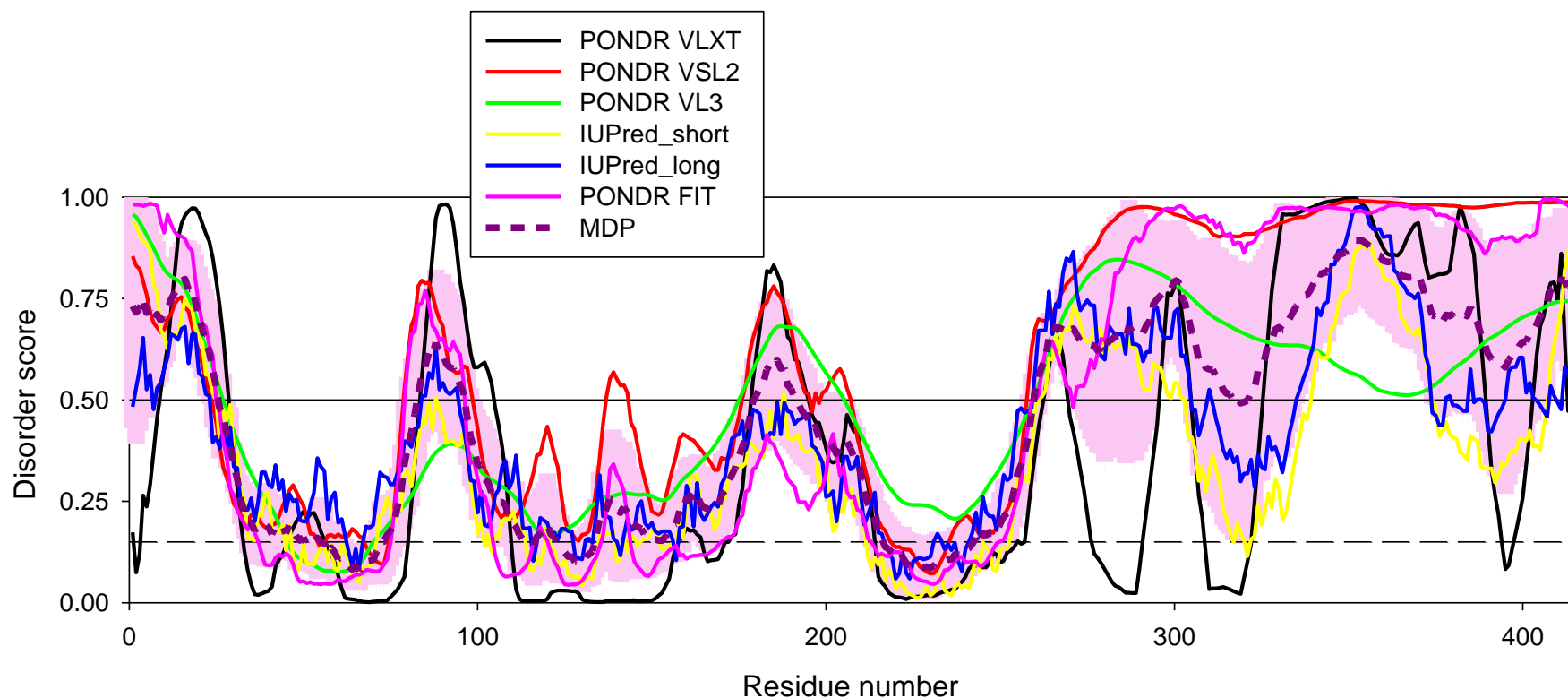
All supplementary figures have identical structural organization, where panel **A** shows the amino acid sequence of the query protein in FASTA format, panel **B** represents the RIDAO-generated disorder profile, panel **C** shows the D<sup>2</sup>P<sup>2</sup>-generated functional disorder profile (where available), panel **D** gives the FuzDrop output, panel **E** represents the AlphaFold2-generated structure with FuzDrop annotations (where available), panel **F** represents the STRING-generated PPI network with corresponding statistics (where available), panel **G** shows the MeDor output and panel **H** shows the plot of the *per* residue disorder score (as provided by PONDR® VLS2) *versus* (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score. For detailed information on the RIDAO and MeDor outputs see Figure 3 legend.

**Supplementary Figure S1.** Functional disorder in TAR DNA-binding protein 43. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the *per residue disorder score* (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

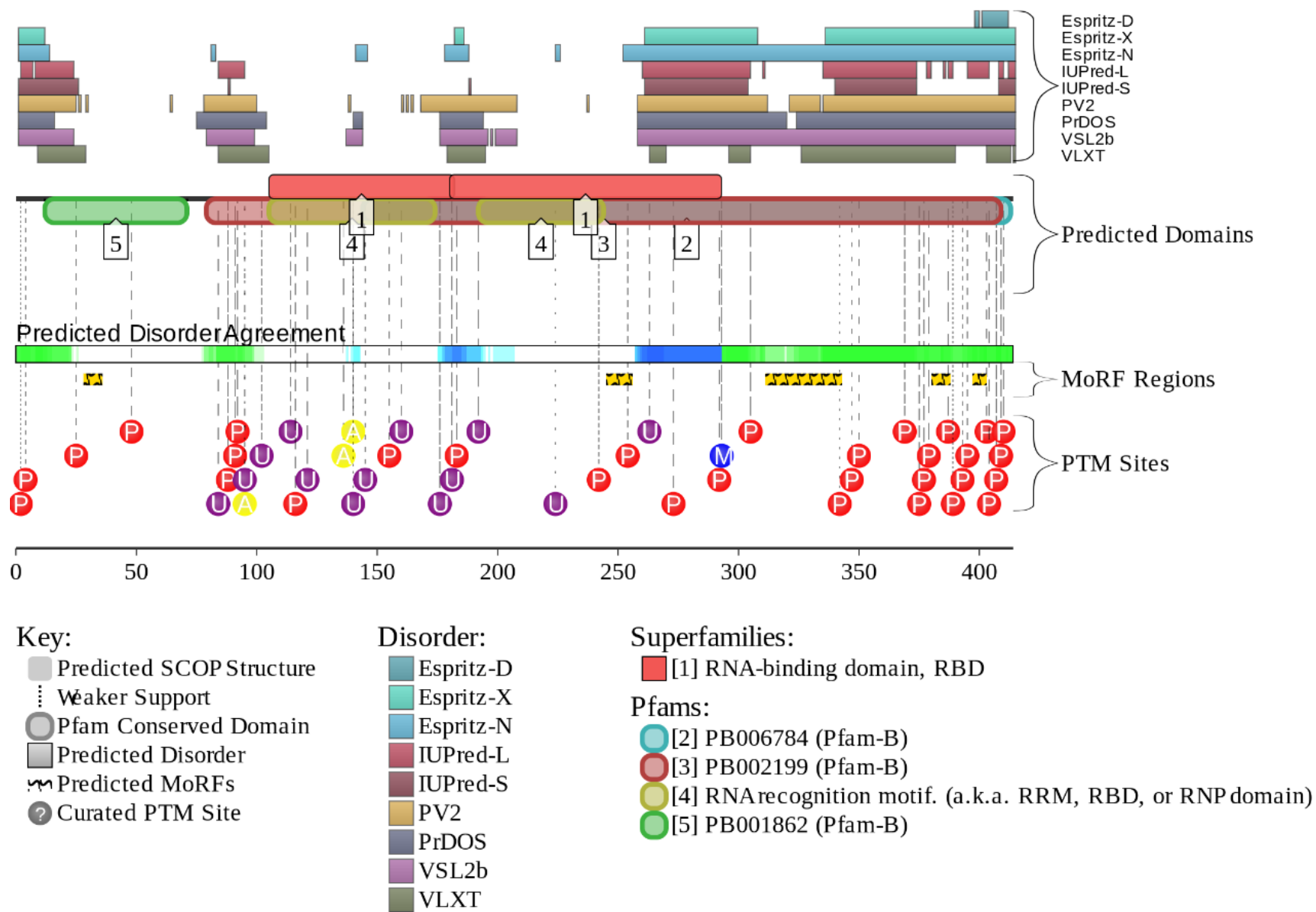
**A**

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MSEYIRVTEDENDEPIEIPSEDDGTVLLSTVTAQFPGACGLRYRNPVSQCMRGVRLVEGILHAPDAGWGNLVYVVNYPKDNKRKMDETDASSAVKVKRAVQKTS
DLIVLGLPWKTTEQDLKEYFSTFGEVLMVQVKDLKTGHSGKGFVRFTEYETQVKVMSQRHMDGRWCCKLPNSKQSQDEPLRSRKVFVGRCTEDMTEDELREFFS
QYGDVMDVFIKPKPFRAFAFVTFADQIAQSLCGEDLIKGISVHISNAEPKHNSNRQLERSGRFGGNPGGFGNQQGGFGNSRGGGAGLGNNQGSNMGGGMNFGAFS
INPAMMAAAQAALQSSWGMMGMLASQQNQSGPSGNNQNGQNMQREPQNQAFGSGNNSYSGSNSGAAIGWGSASNAGSGSGFNGGFGSSMDSKSSGWGM
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**B**



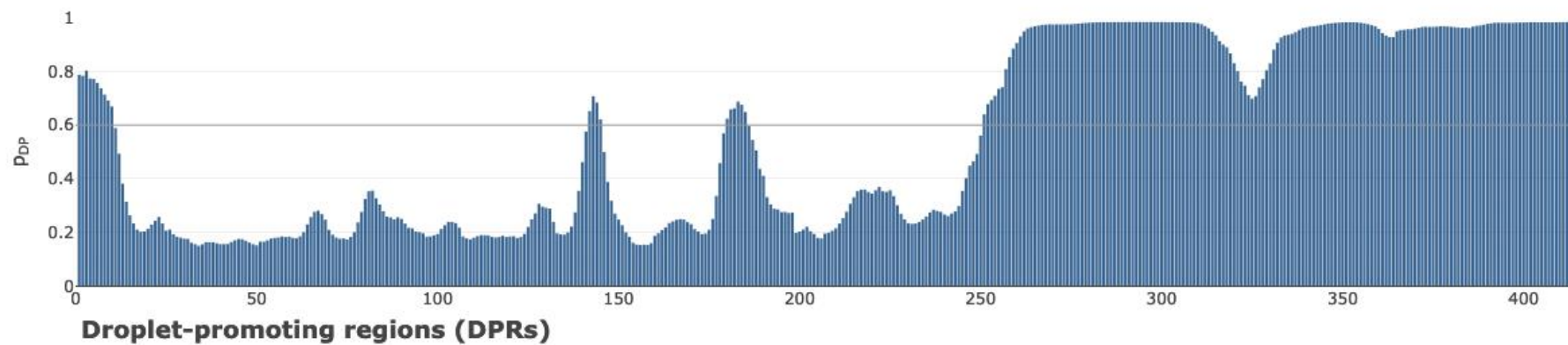
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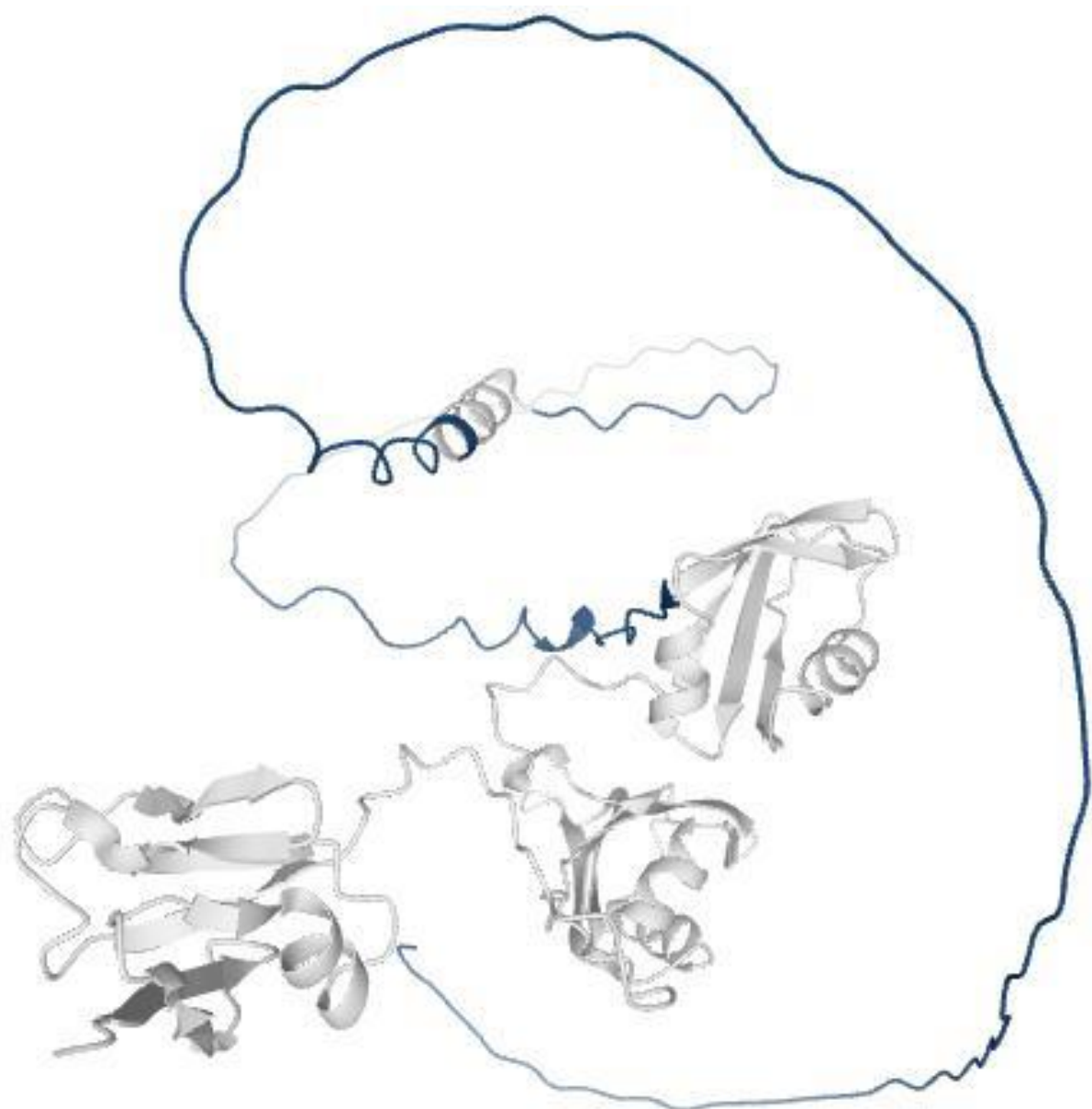
D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.8981$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**



**Aggregation hot-spots**









minimum required interaction score: high confidence (0.700)

number of nodes: 88

number of edges: 1297

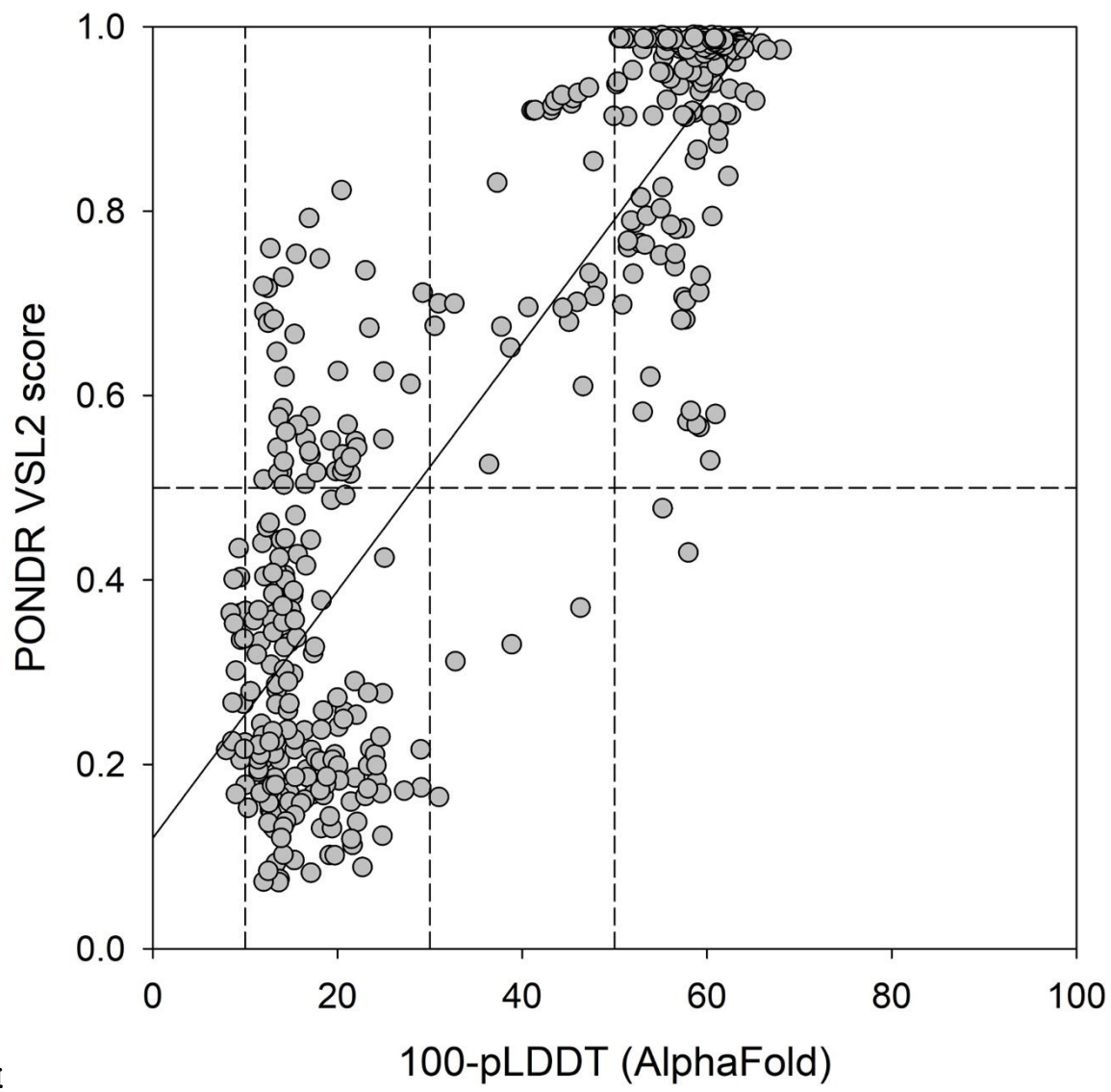
average node degree: 29.5

avg. local clustering coefficient: 0.795

expected number of edges: 159

PPI enrichment p-value:  $< 1.0e-16$





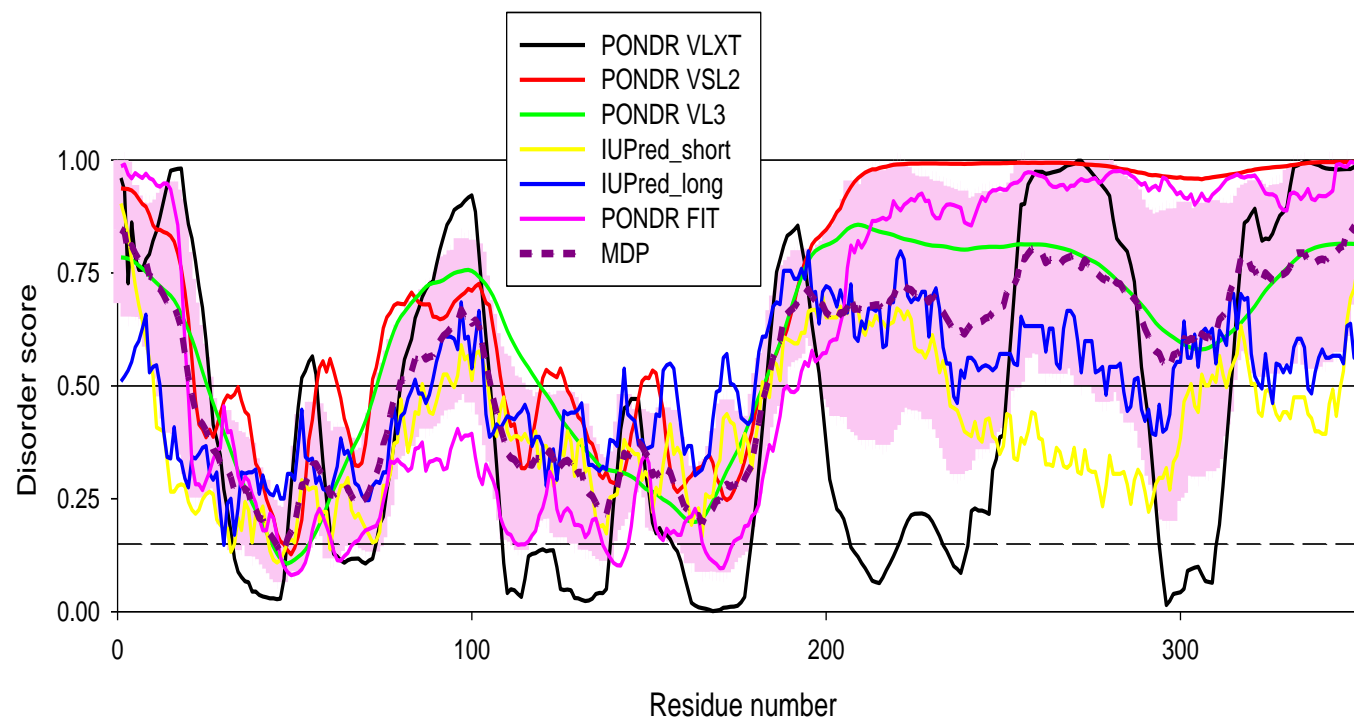
H

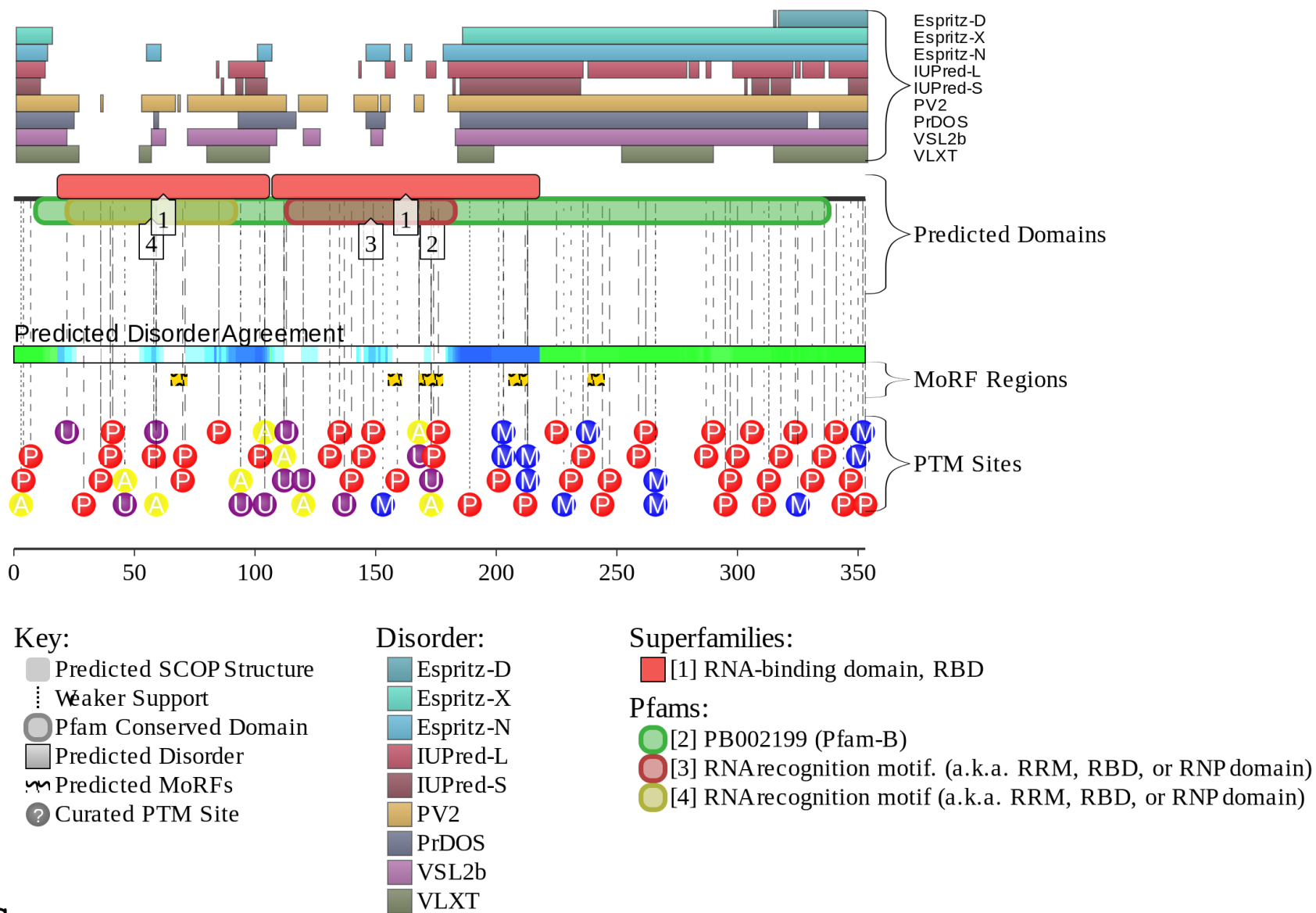
**Supplementary Figure S2.** Functional disorder in heterogeneous nuclear ribonucleoproteins A2/B1. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>sp|P22626|ROA2_HUMAN Heterogeneous nuclear ribonucleoproteins A2/B1 OS=Homo sapiens OX=9606 GN=HNRNPA2B1 PE=1 SV=2
MEKTLETVPLERKKREKEQFRKLFIGGLSFETTEESLRNYEQWGKLTDCVVMRDPASKRSRGFGFVTFSSMAEVDAAAMAARPHSIDGRVVEPKRAVAREESGKPGAHVTVKKLFVGG
IKEDTEEHHLRDYFEEYGKIDTIEIITDRQSGKKRGFGFVTFDDHDPVDKIVLQKYHTINGHNAEVRKALSRQEMQEVQSSRSRGGNFGFGDSRGGGNGFGPGPGSNFRGGS DGYGS
GRGFGDGYNGYGGGPGGNGFGGSPGYGGGRGGYGGGGPGYGNQGGGYGGGYDNYGGGNYGSGNYNDFGNYNQQPSNYGPMKSGNFGGSRNMGGPYGGGNYGPGGSGGSGGYGGRSRY
```

**B**



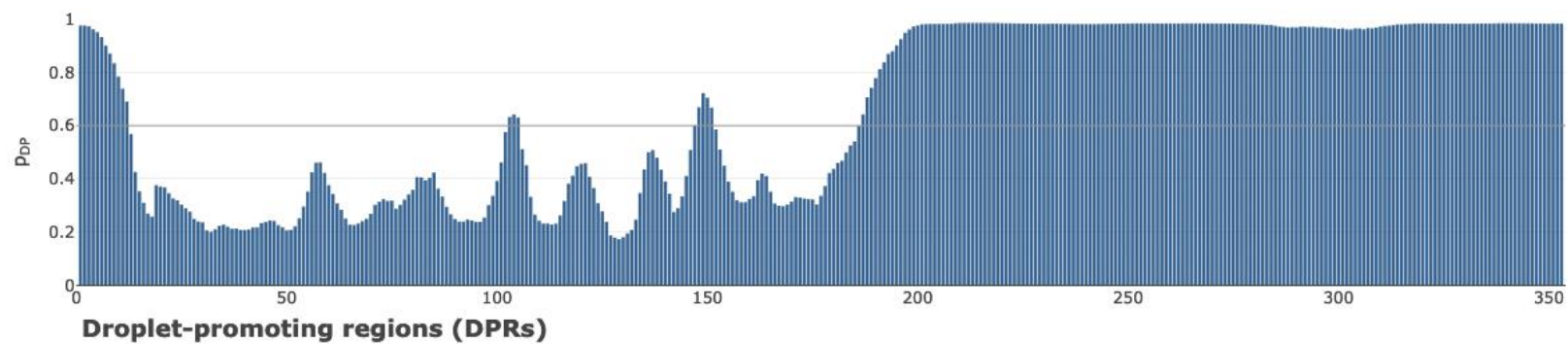


C

D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.9808$

Residue-based droplet-promoting probabilities ( $p_{DP}$ )



1-12



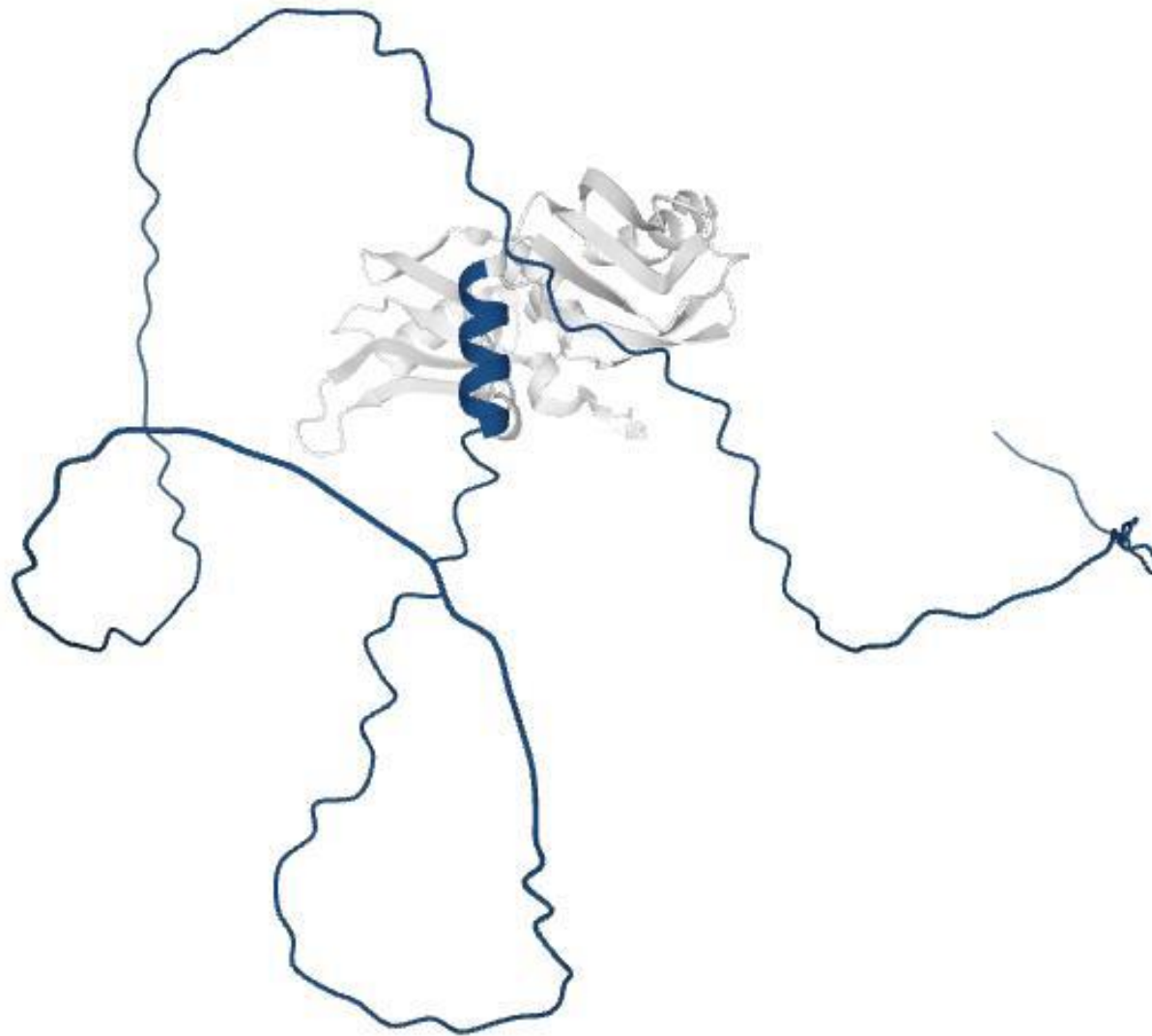
187-353

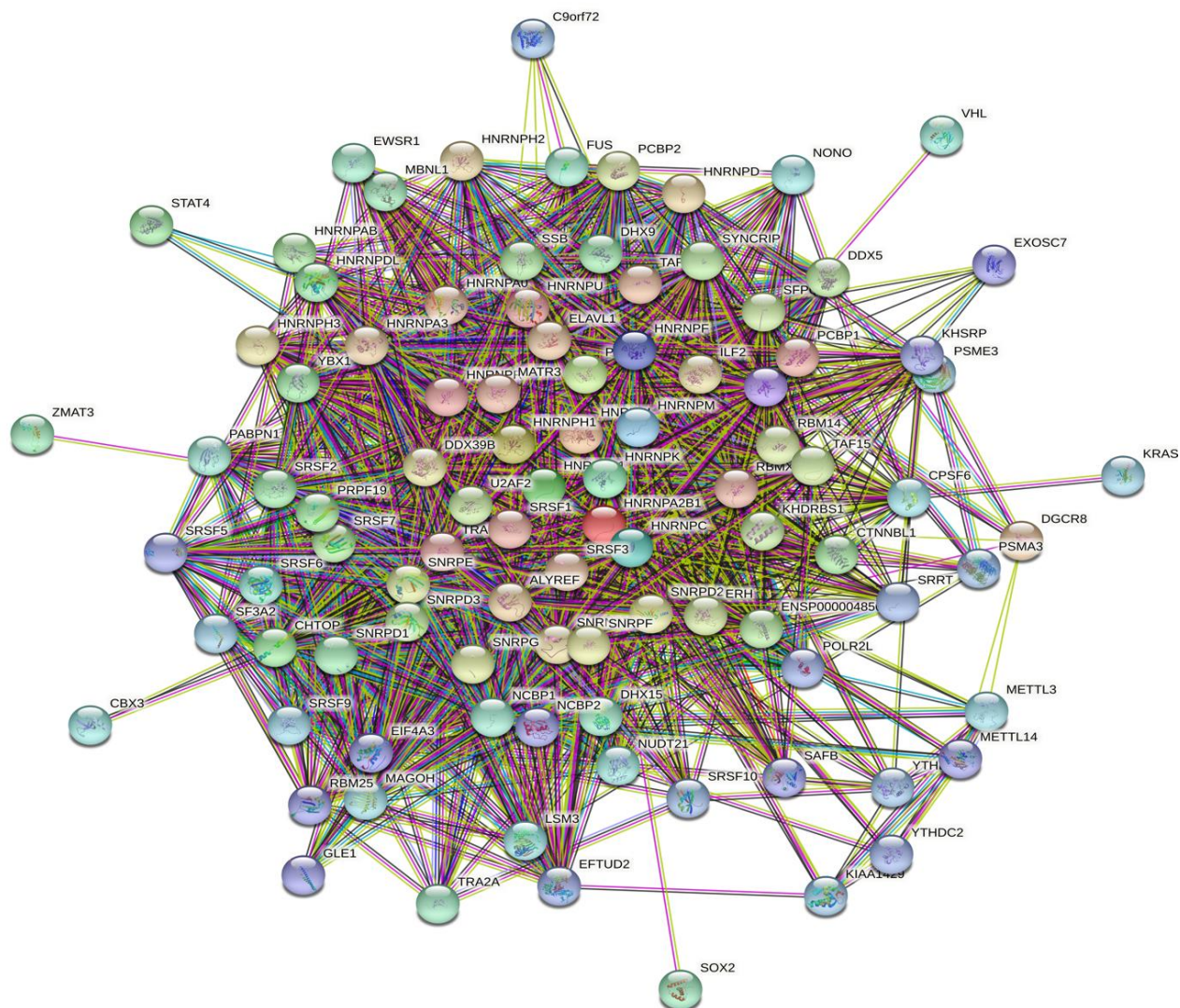


Aggregation hot-spots



**E**



**F**

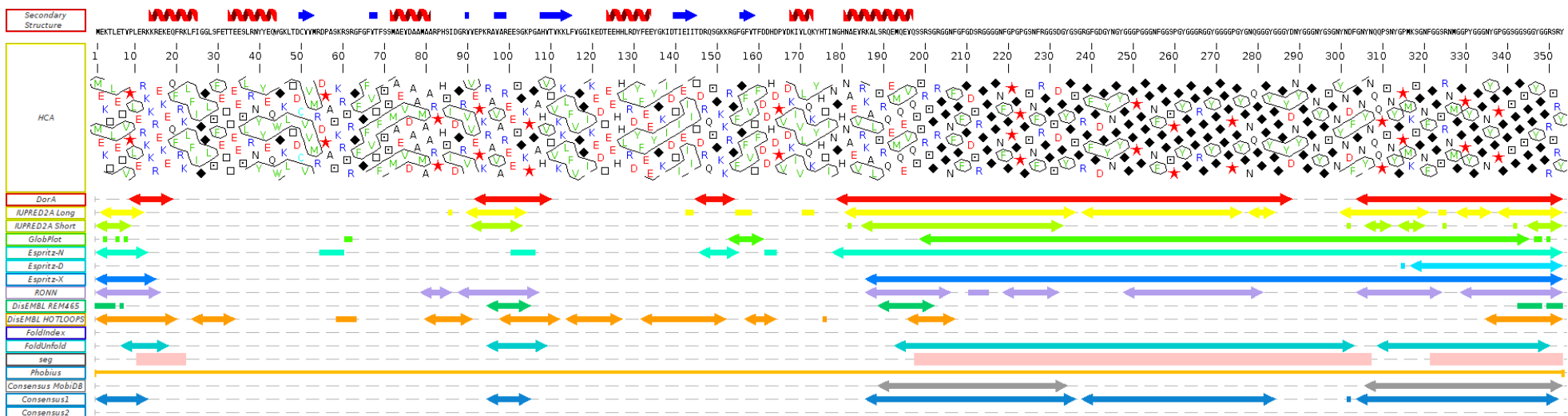
minimum required interaction score: high confidence (0.700)

number of nodes: 97

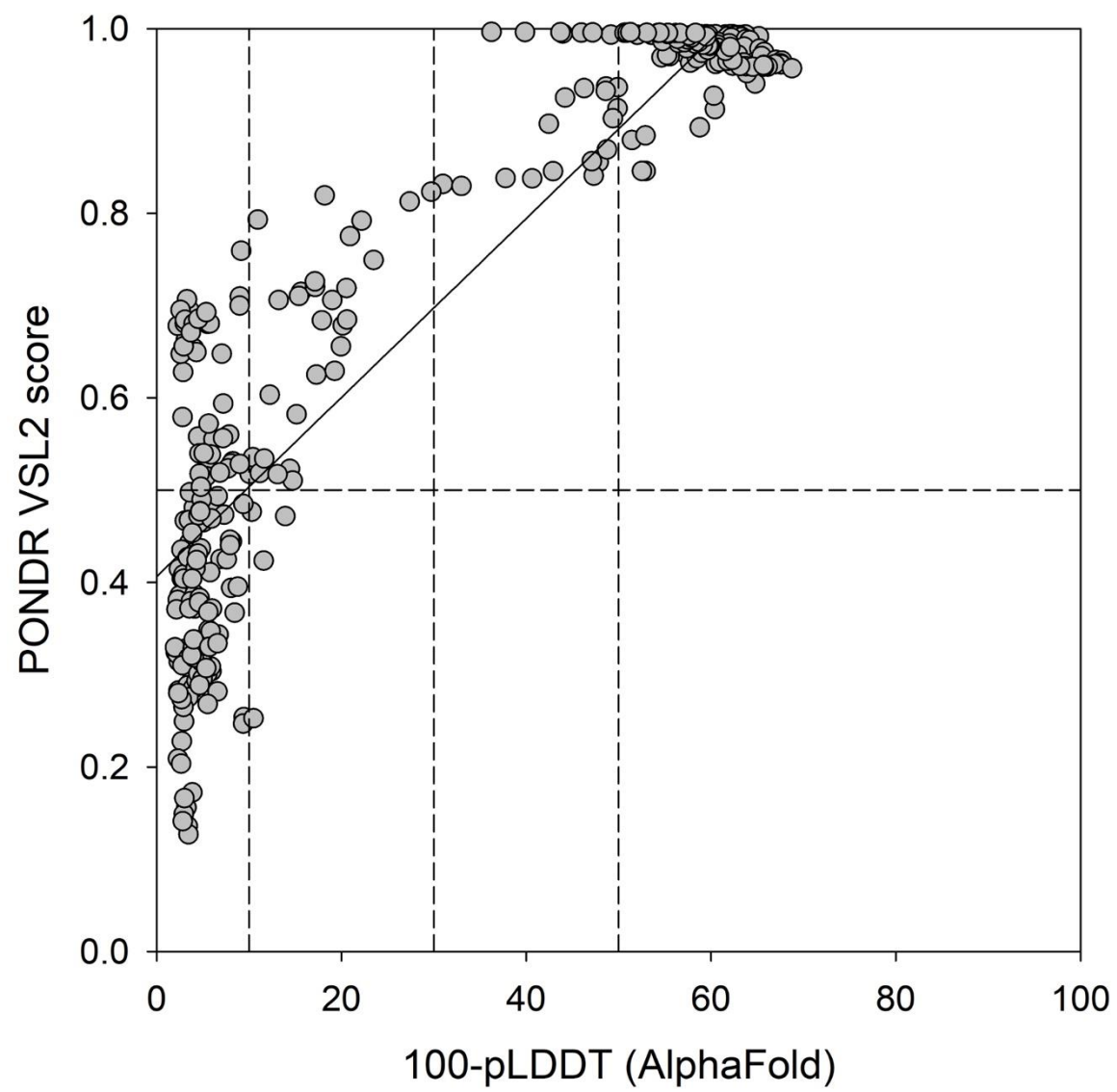


number of edges: 1861  
average node degree: 38.4  
avg. local clustering coefficient: 0.762  
expected number of edges: 193  
PPI enrichment p-value:  $< 1.0e-16$

**G**



H

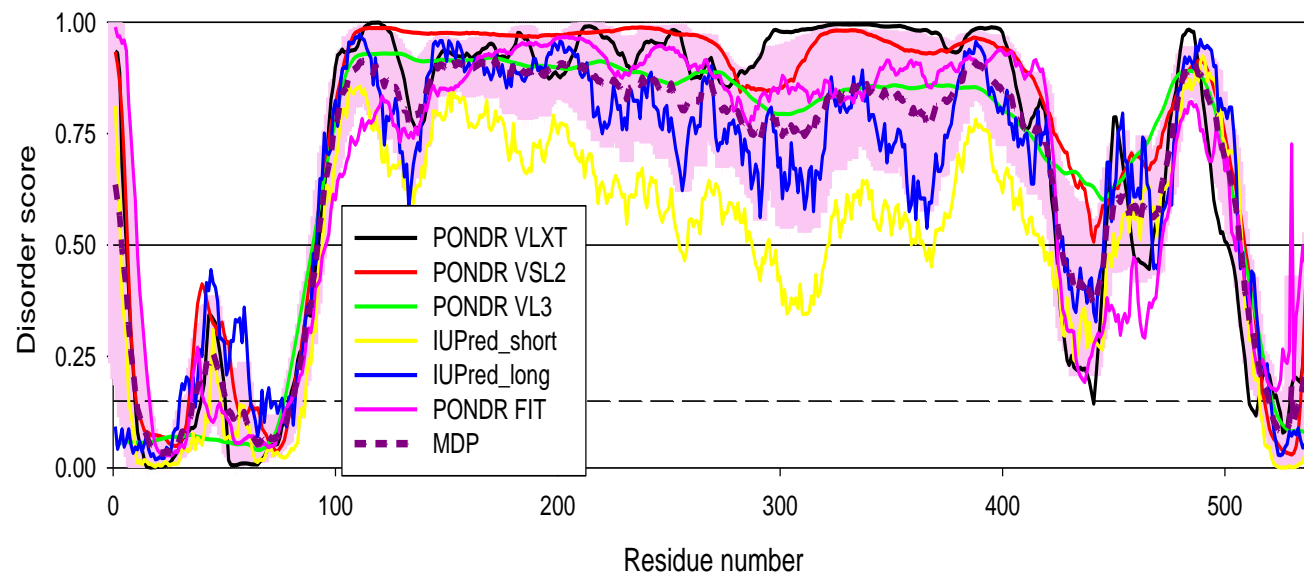


**Supplementary Figure S3.** Functional disorder in mitochondrial antiviral-signaling protein MAVS. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

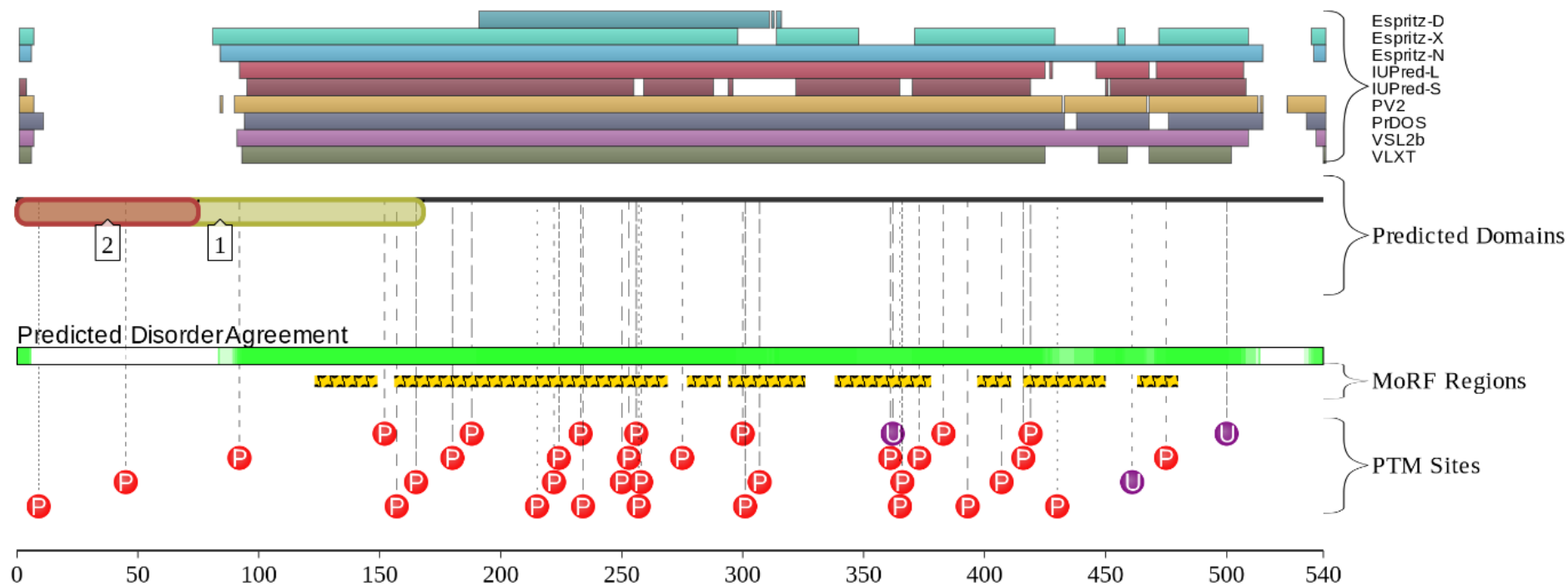
**A**

```
>sp|Q7Z434|MAVS_HUMAN Mitochondrial antiviral-signaling protein OS=Homo sapiens OX=9606 GN=MAVS PE=1 SV=2
MPFAEDKTYKYICRNFNFNCNVDVVEILPYLPCLTARDQDRLRATCTLSGNRDTLWHLFNTLQRRPGWVEYFIAALRGCELVDLADEVASVYQSYQPTSDRPPDPLEPPSLPAERPG
PPTPAAAHISIPYNSCREKEPSYPMPVQETQAPESPGENSEQALQTLSPRAIPRNPDDGGPLESSDLAALSPLTSSGHQEQDTELGSTHTAGATSSLTSPSRGPVSPSVSFQPLARSTPR
ASRLPGPTGSVVSTGTSTFSSSSPGLASAGAAEGKQGAESDQAEPIICSSGAEAPANSLPSKVPTTLMPTVNTVALKV PANPASVSTVPSKLP TSSKPPGAVPSNALTNPAPSKLPINST
RAGMVPSKVPTSMVLTKVSASTVPTDGSSRNEETPAAPT PAGATGGSSAWLDSSSENRLGLSEL SKPGVLASQVDSPFSGCFEDLAISASTSLGMGPCHGPEENEYKSEGTFGIHVAE
NPSIQLLEGNPGPPADPDGGPRPQADRKFQEREVPCHRSPGALWLQVAVTGVLVVTLLVLVLYRRRLH
```

**B**



C



Key:

- Predicted SCOP Structure
- Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- Predicted MoRFs
- Curated PTM Site

Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

Superfamilies:

N/A No Hits

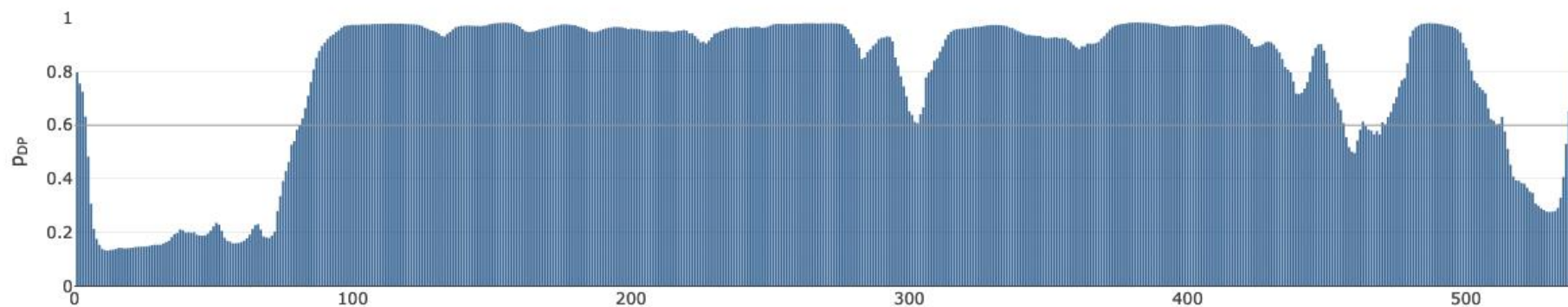
Pfams:

- [1] PB006841 (Pfam-B)
- [2] PB013822 (Pfam-B)

D

Probability of spontaneous liquid-liquid phase separation:  $p_{\text{LLPS}} = 0.9996$

**Residue-based droplet-promoting probabilities ( $p_{\text{DP}}$ )**



**Droplet-promoting regions (DPRs)**

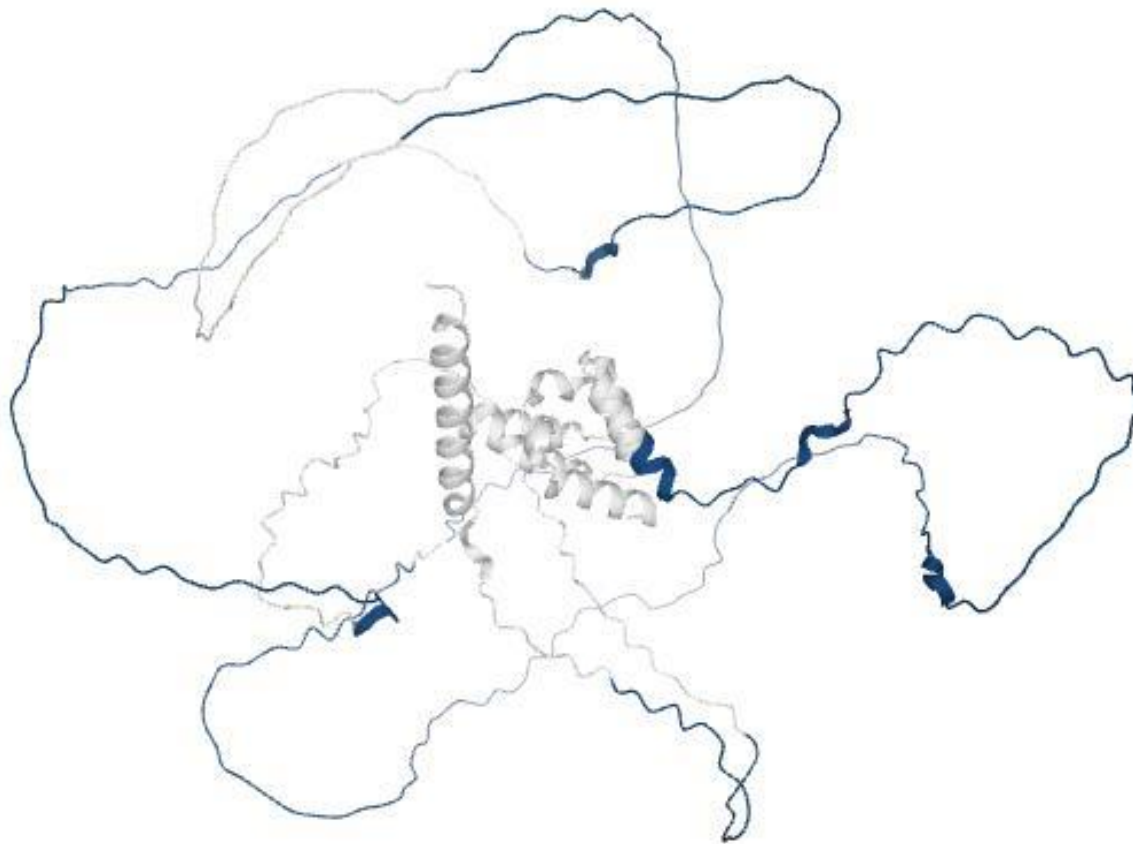


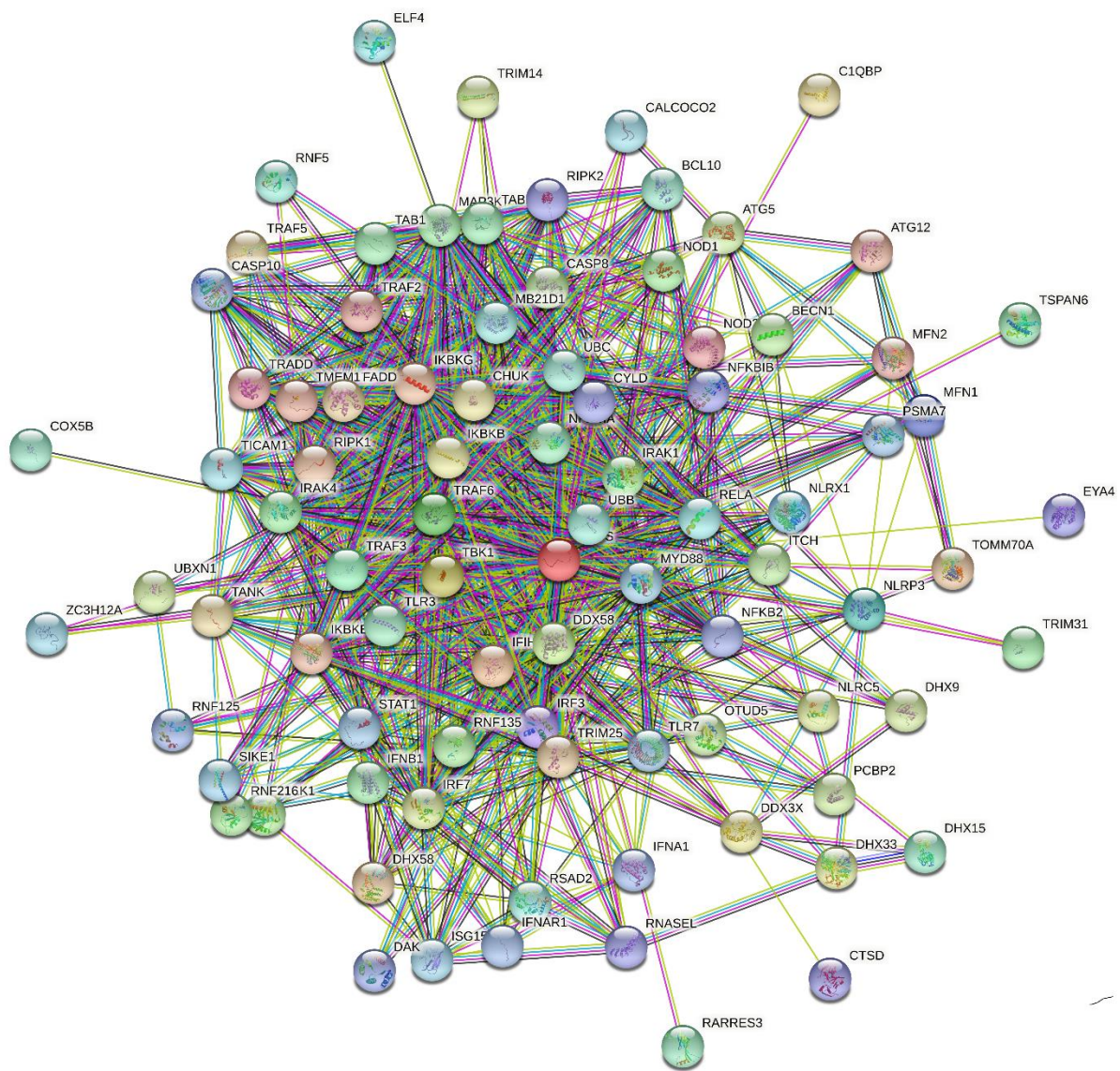
**Aggregation hot-spots**





**E**



**F**

minimum required interaction score: high confidence (0.700)

number of nodes: 87

number of edges: 786

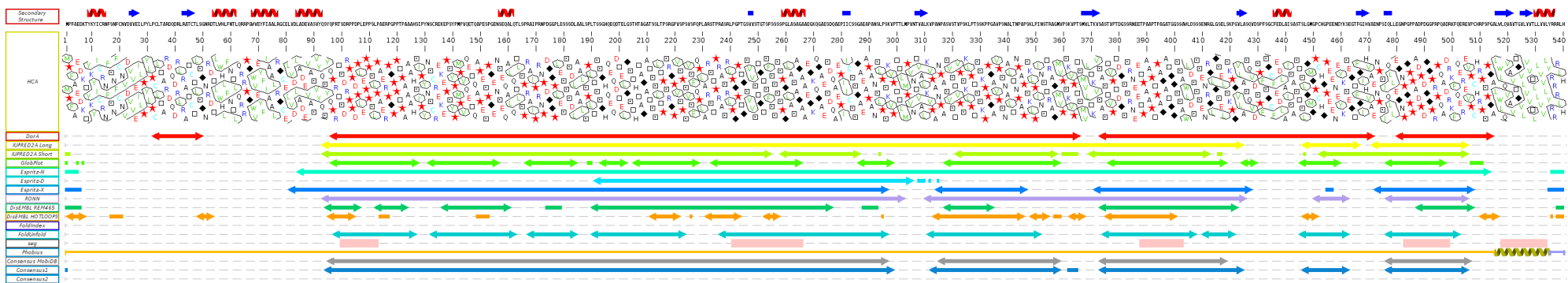
average node degree: 18.1

avg. local clustering coefficient: 0.7

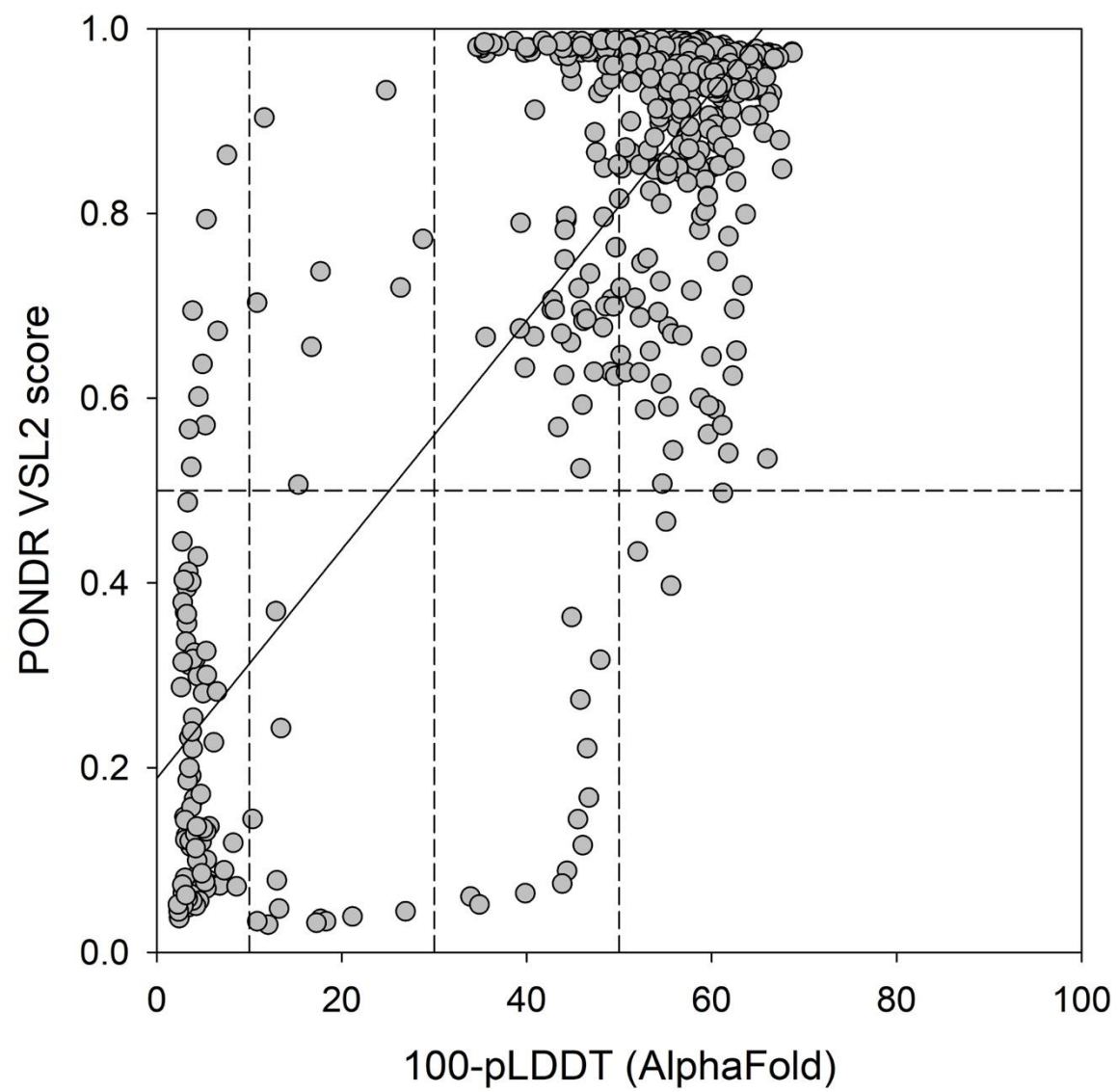
expected number of edges: 151

PPI enrichment p-value:  $< 1.0e-16$

**G**



H

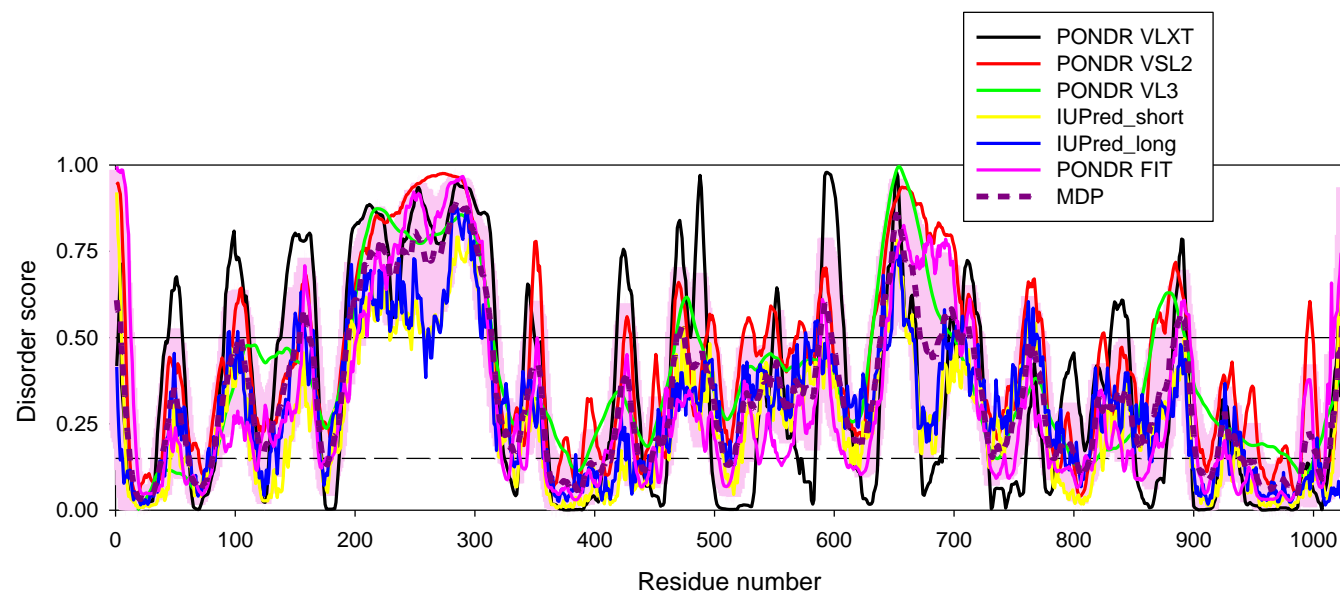


**Supplementary Figure S4.** Functional disorder in interferon-induced helicase C domain-containing protein 1, MDA5. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

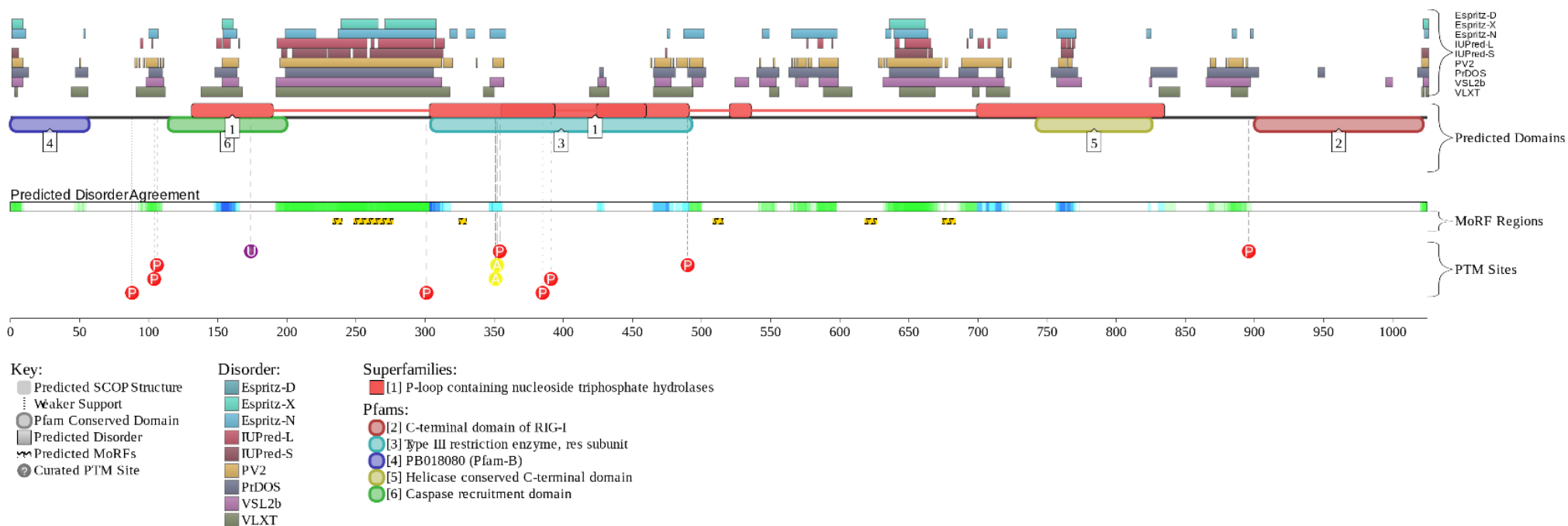
```
>sp|Q9BYX4|IFIH1_HUMAN Interferon-induced helicase C domain-containing protein 1 OS=Homo sapiens OX=9606 GN=IFIH1 PE=1
SV=3
MSGYSTDENFRYLISCFRARVKMYIQVEPVLDTFLPAEVKEQIQRTVATSGNMQAVELLSTLEKGVWHLGWTREFVEALRRTGSPLAARYMNPETDLPSPSFENAHDEYLQLL
NLLQPTLVDKLLVRDVLDKMEEELLTIEDNRNIAAAENNGNESGVRELLKRIVQKENWFS AFLNVLRQTGNNELVQELTGSDCSESNAE IENLSQVDG PQVEEQLLSTTVQPNLEKE
VWGMENSSSESSFADSSVSESDTSLAEGSVSCLDESLGHNSNMGSDSGTMGSDSDEENVAARASPEPELQLRPYQMEVAQPALEGKNI IICLPTGSGKTRVAVYIAKDHLDKKKKAS
EPGKVIVLVNKKVLLVEQLFRKEFPFLKKWYRVIGLSGDTQLKISFPEVVKSCDIIISTAQILENSLLNLENGEDAGVQLSDFSLIIIDECHHTNKEAVYNNIMRHYLMQKLKNNRLK
KENKPVIPLPQILGLTASPGVGATKQAKAEHILKLCANLDAFTIKTVKENLDQLKNQIQEPCKKFAIADATREDPFKEKLEIMTRIQTTCQMSPMSDFGTQPYEQWAIQMEKKAA
KEGNRKERVCAEHLRKYNEALQINDTIRMIDAYTHLETIFYNEEKDKKFAVIEDDSDEGGDDEYCDGDEDEDDLKPLKLDDETDRFLMTLFFENNKMLKRLAENPEYENEKLTCLRNTI
MEQYTRTEESARGIIFTKTRQSAYALSQWITENEKFAEVGVKAHHLIGAGHSSEFKPMTQNEQKEVISKFRTGKINLLIATTVAEEGLDIKECNIVIRYGLVTNEIAMVQARGRAD
ESTYVLVAHSGSGVIEHETVNDFREKMMYKAIHCVQNMKPEEYAHKILELQMQSIMEKKMKTKRNI AKHYKNNPSLITFLCKNCSVLACSGEDIHVIEKMHVNMTPFEFKELYIVREN
KALQKKCADYQINGEIIICKCGQAWGTMVMVHKGLDLPCLKIRNFVVVFKNNS TKKQYKKWVELPITFPNLDYSECCLFSDED
```

**B**



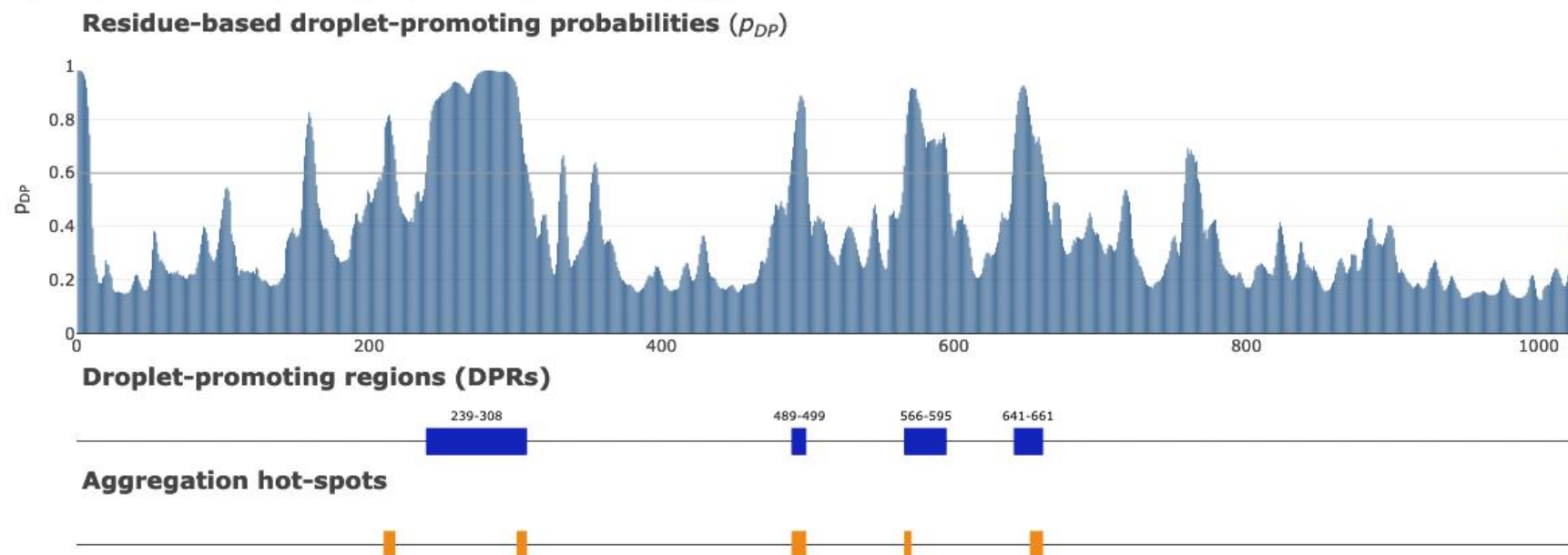


C



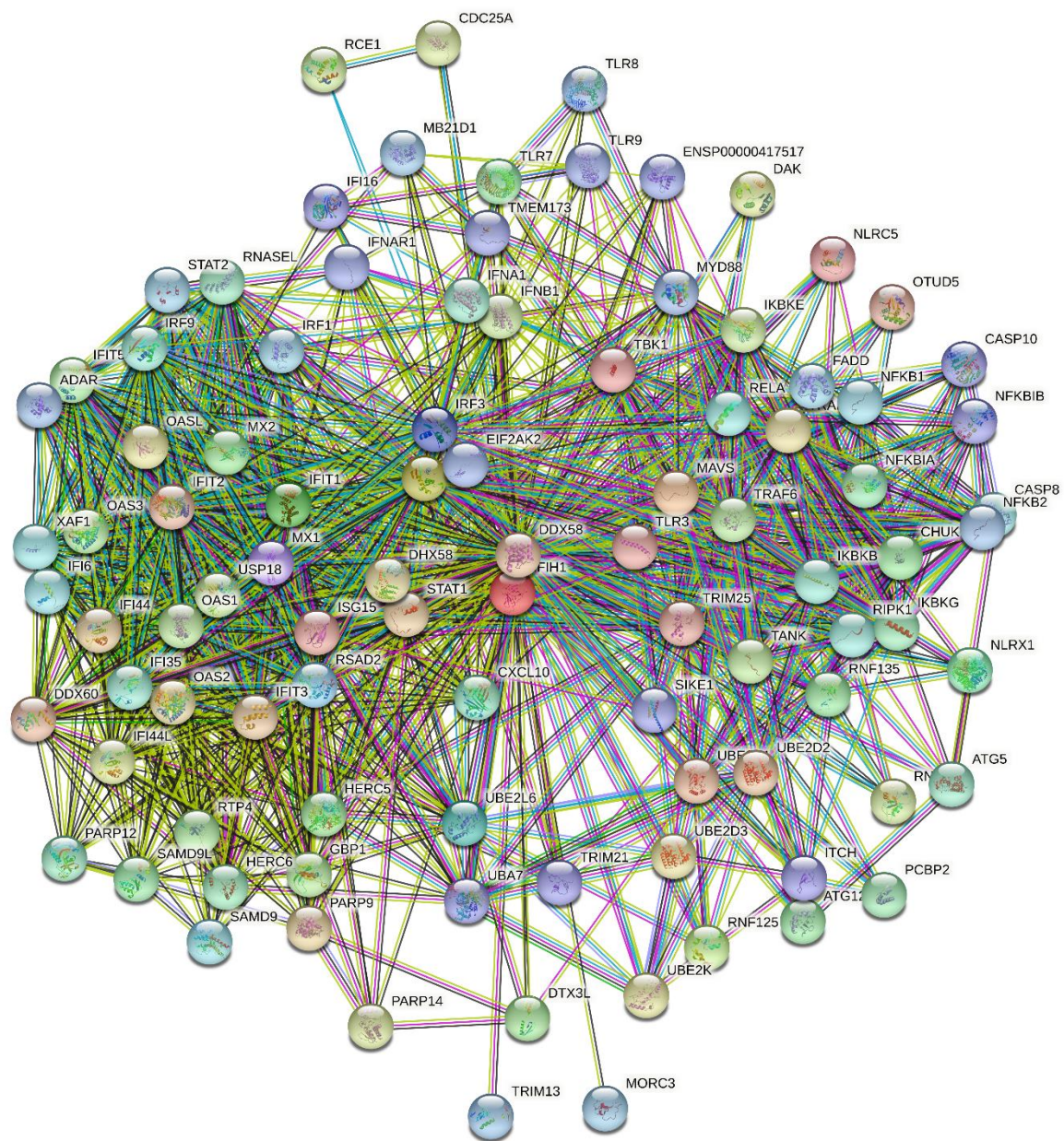
**D**

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.6164$



**E**

There is no AlphaFold2-generated structure for this protein at FuzDrop



minimum required interaction score: high confidence (0.700)

number of nodes: 96

number of edges: 1162

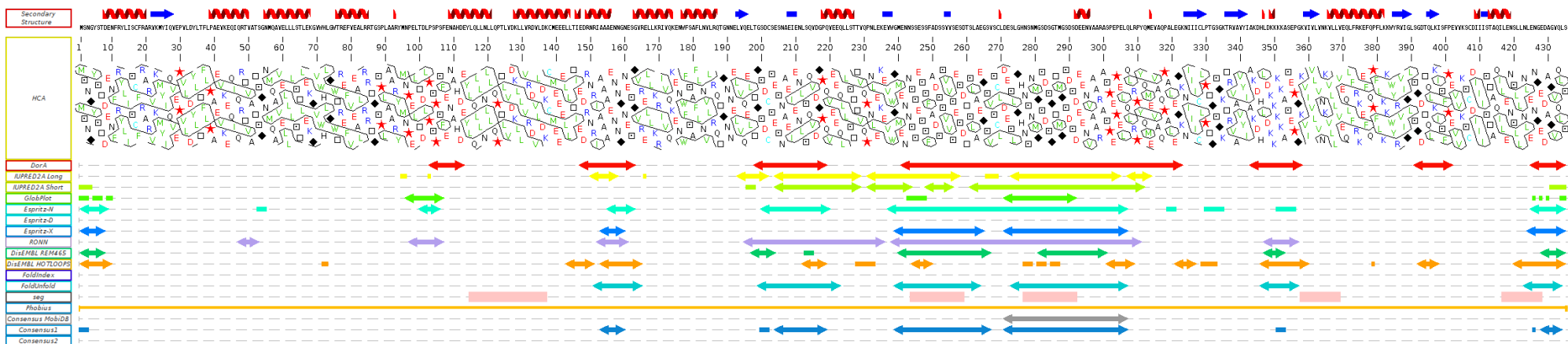
average node degree: 24.2

avg. local clustering coefficient: 0.751

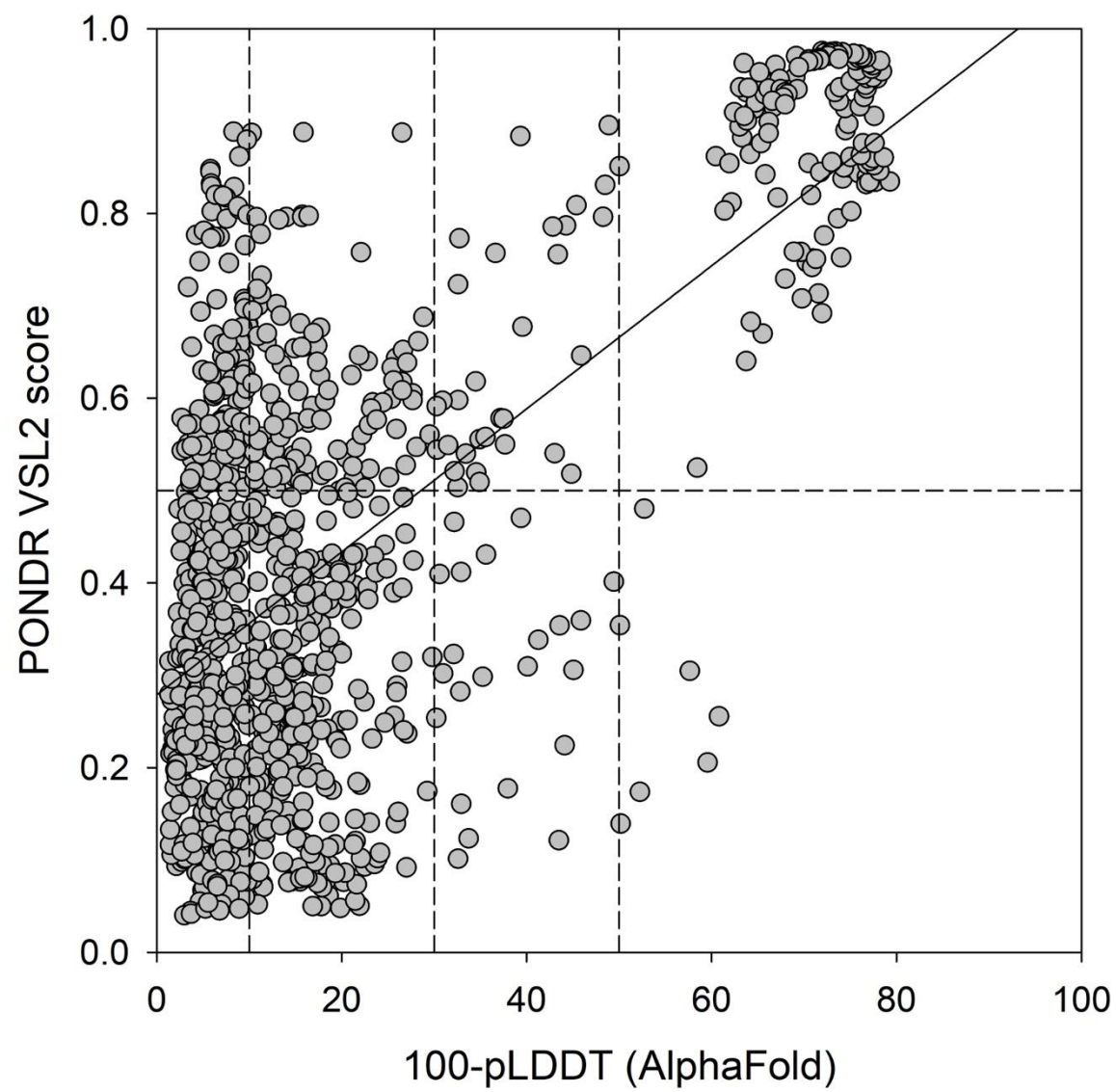
expected number of edges: 146

PPI enrichment p-value:  $< 1.0e-16$

## G



H



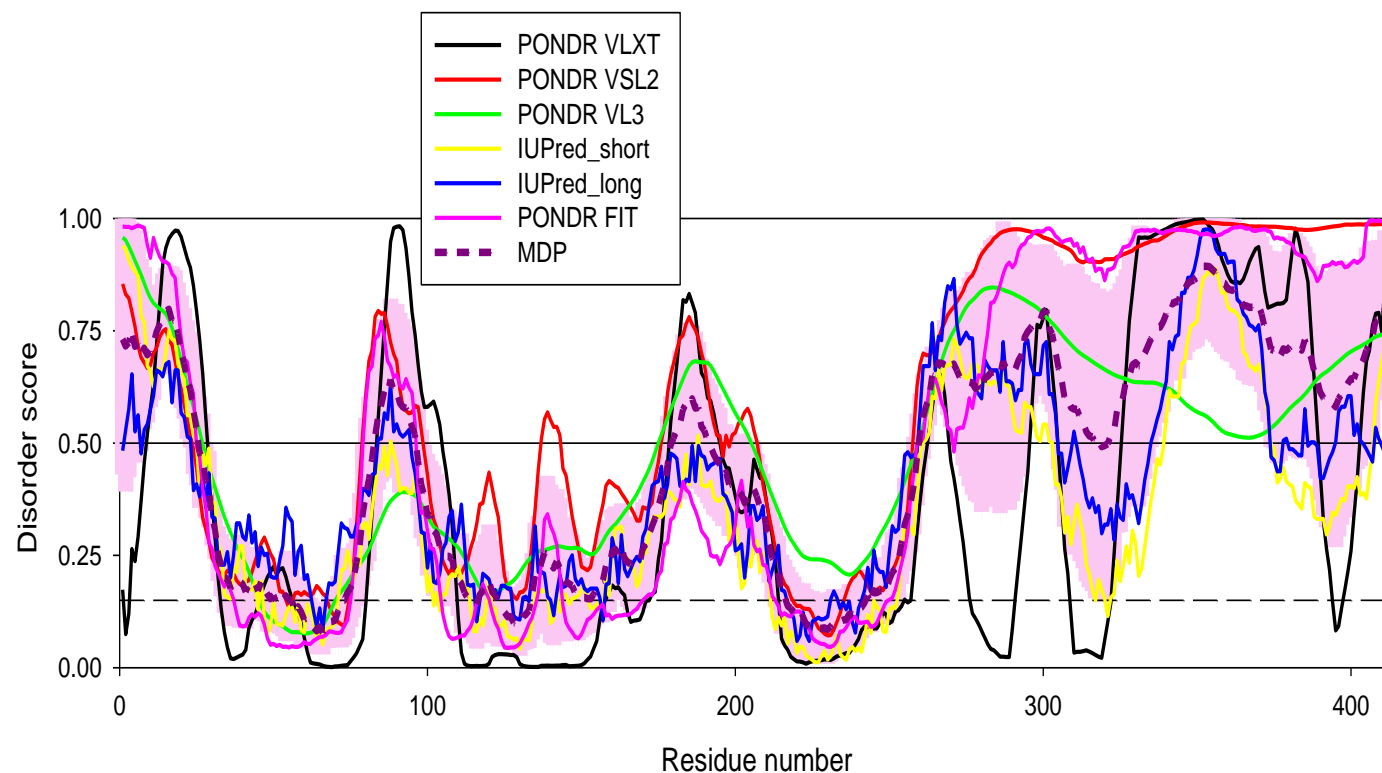


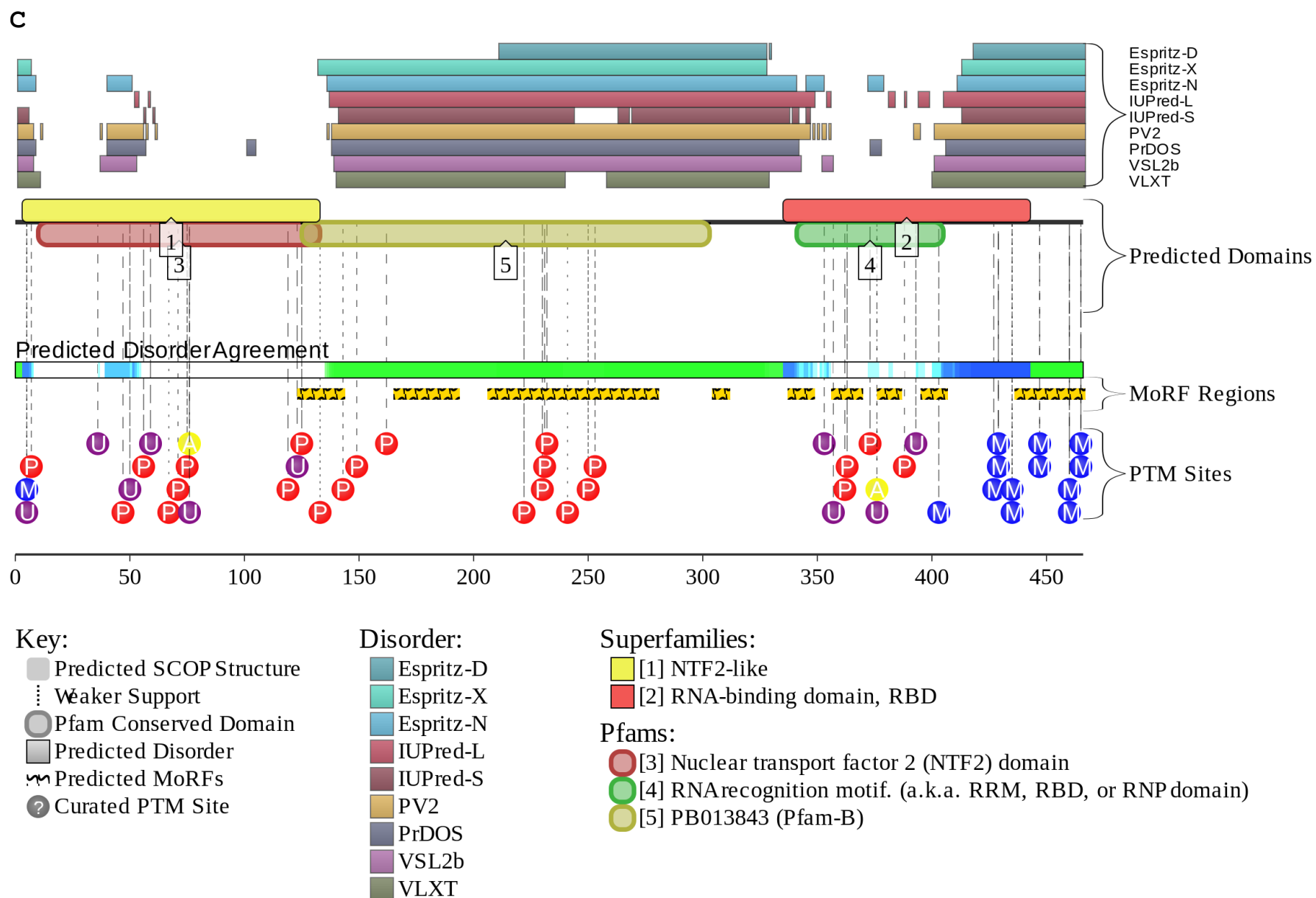
**Supplementary Figure S5.** Functional disorder in Ras GTPase-activating protein-binding protein 1, G3BP1. **A.** Amino acid sequence. **B.** RDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>sp|Q13283|G3BP1_HUMAN Ras GTPase-activating protein-binding protein 1 OS=Homo sapiens OX=9606 GN=G3BP1 PE=1 SV=1
MVMEKPSPLLVGREFVRQYYTLLNQAPDMLHRFYGKNSSYVHGGLDSNGKPADAVYGQKEIHRKVMSQNFTNCHTKIRHVDAHATLNDGVVVQVMGLLSNNNQALRRFMQTFVLAPEG
SVANKFYVHNDIFRYQDEVFGGFVTEPQEESEEEVEEPEERQQTPEVVPDDSGTFYDQAVVSNDMEEHLEEPVAEPEPDPEPEPEQEPVSEIQEEKPEPVLEETAPEDAQKSSSPAPA
DIAQTVQEDLRTFSWASVTSKNLPPSGAVPVTGIPPHVVKVPASQPRPESKPESQIPPQRQDQVRVREQRINIPQGRPRPIREAGEQGDIEPRRMVRHPDSHQLFIGNLPHEVDKS
ELKDFQSYGNVVELRINSGGKLPNFGFVVFDDSEPVQKVLNRPIMFRGEVRLNVEEKKTRAAREGDRRDNRRLRGPGGPRGGLGGGMRGPPRGGMVQKPGFGVGRGLAPRQ
```

**B**

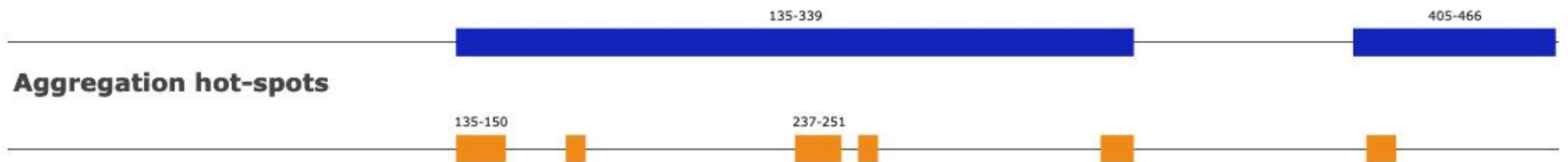
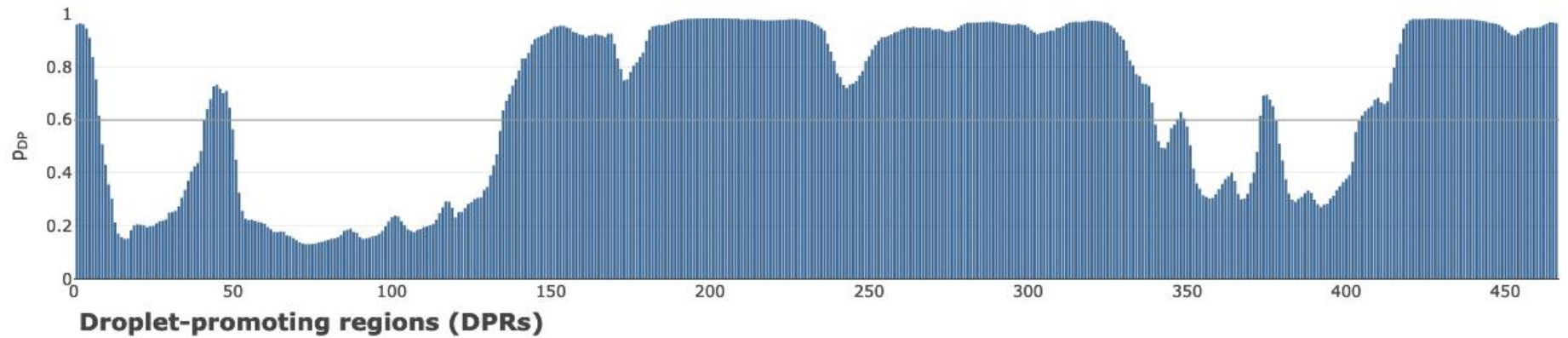




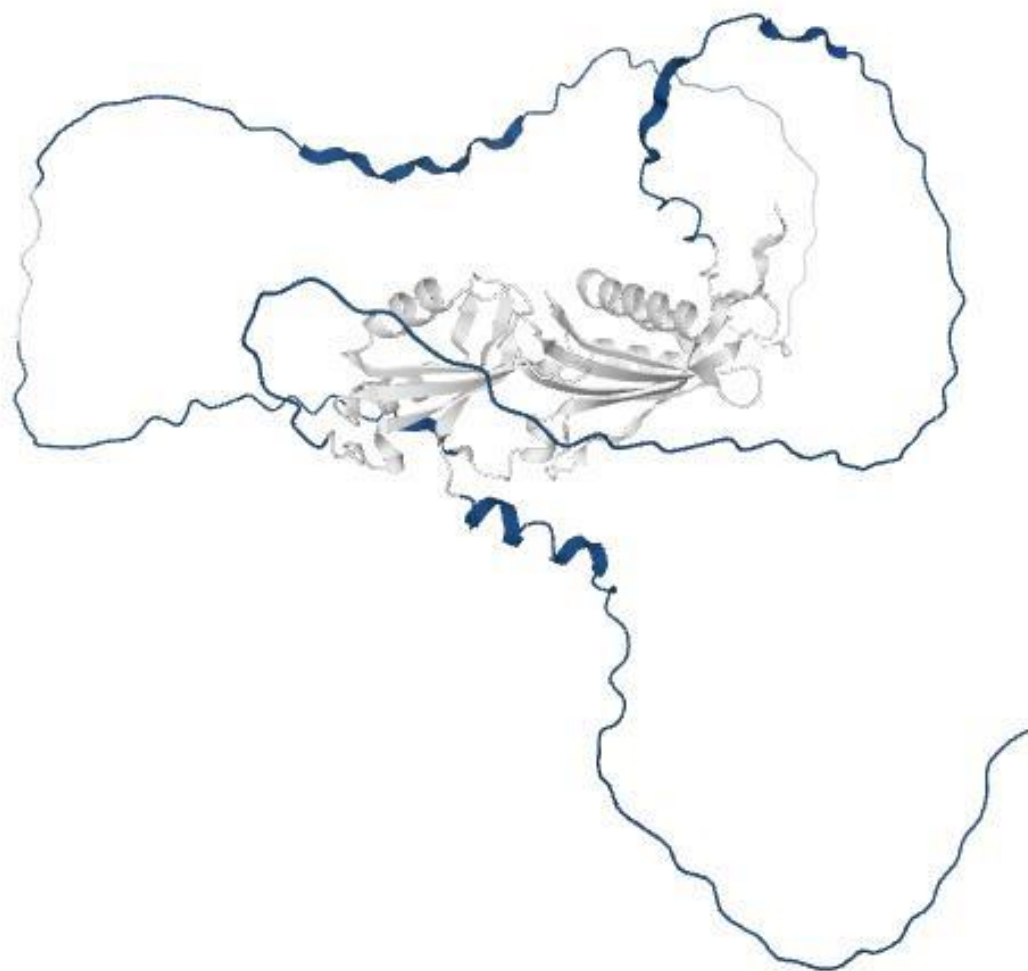
D

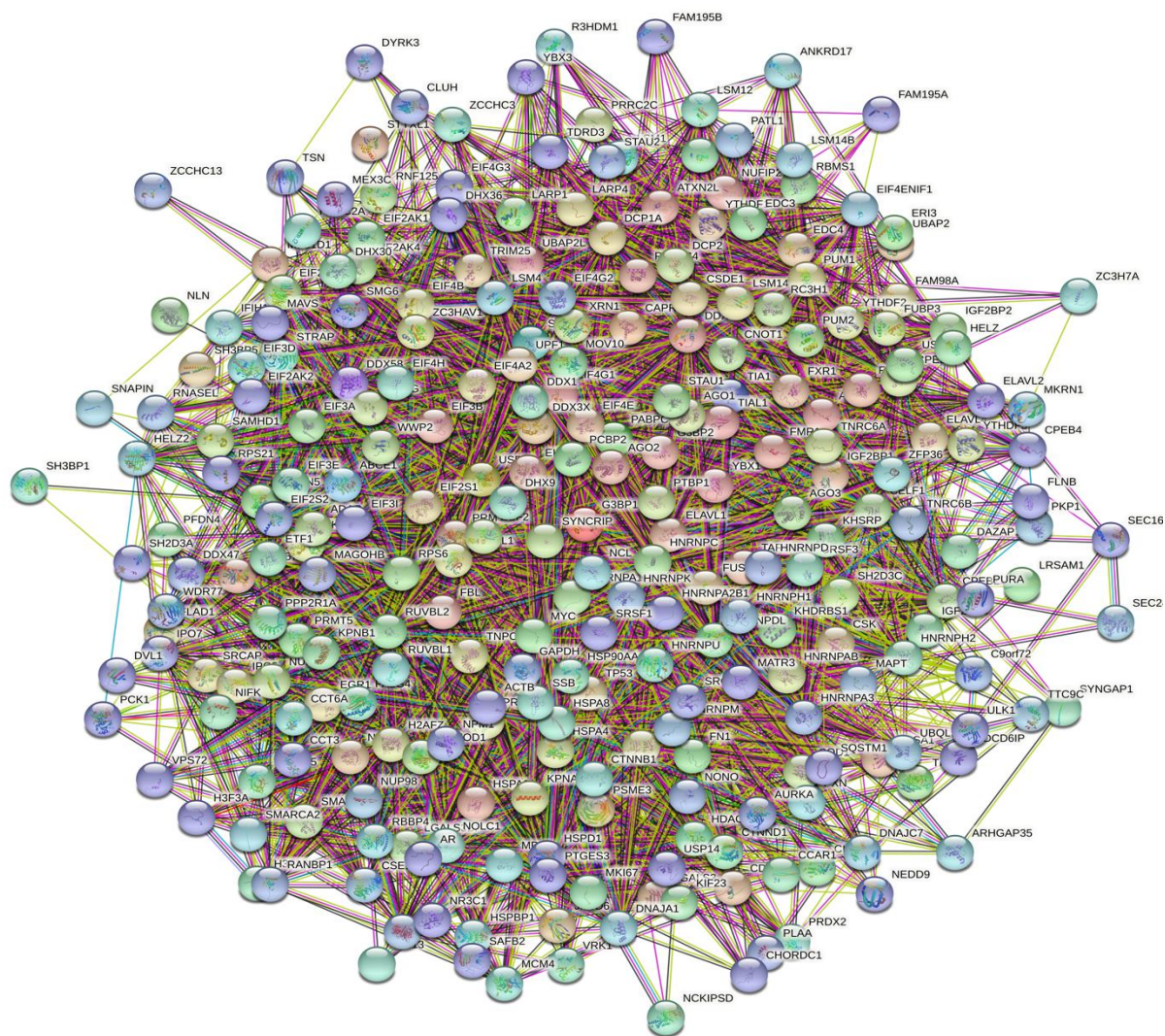
Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.9937$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**



**E**



**F**

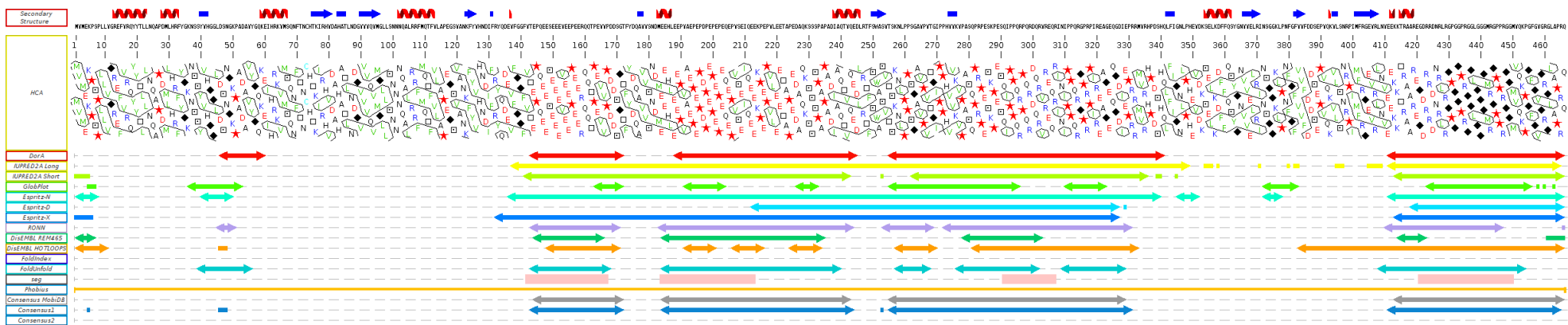
minimum required interaction score: medium confidence (0.400)

number of nodes: 269

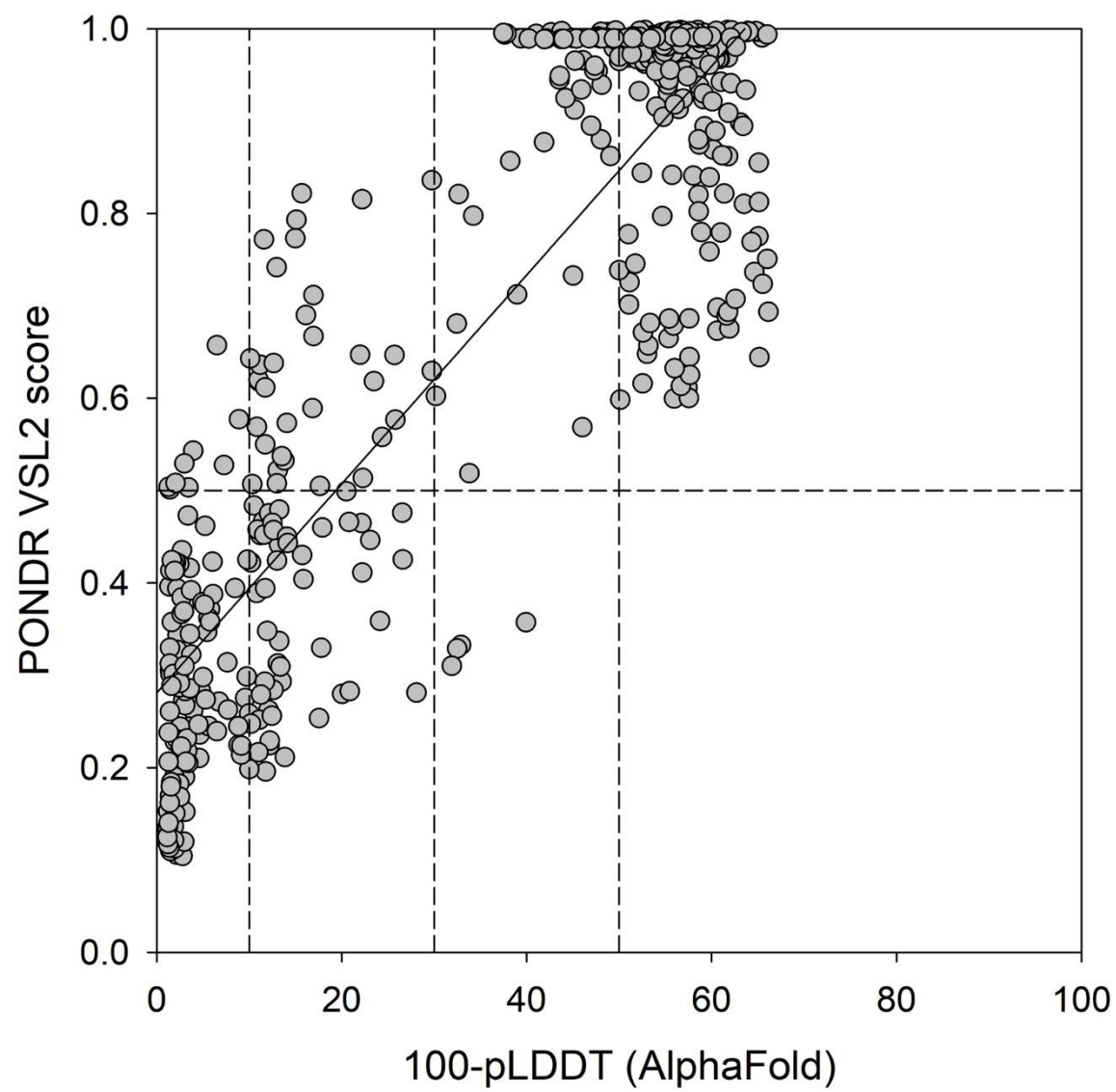
number of edges: 5342  
average node degree: 39.7  
avg. local clustering coefficient: 0.541  
expected number of edges: 1729  
PPI enrichment p-value:  $< 1.0e-16$



**G**



H

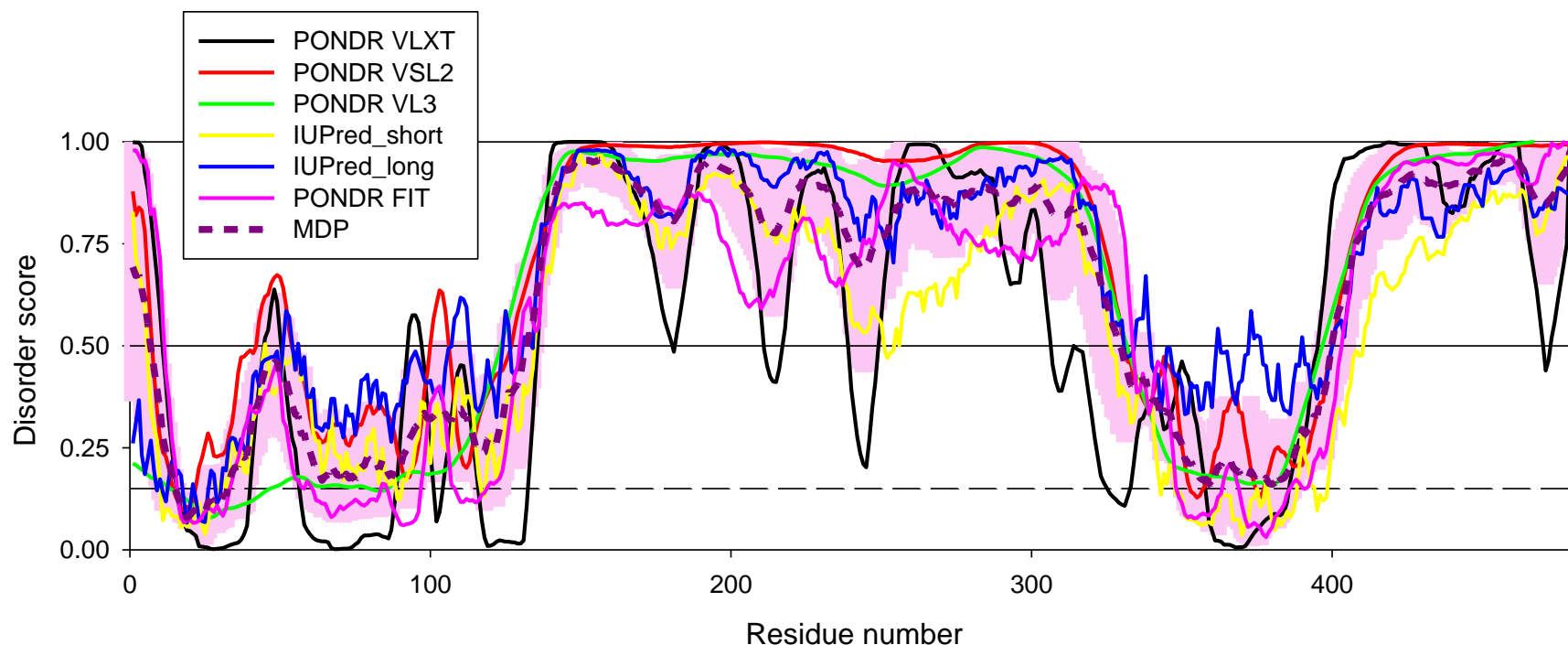


**Supplementary Figure S6.** Functional disorder in Ras GTPase-activating protein-binding protein 2, G3BP2. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

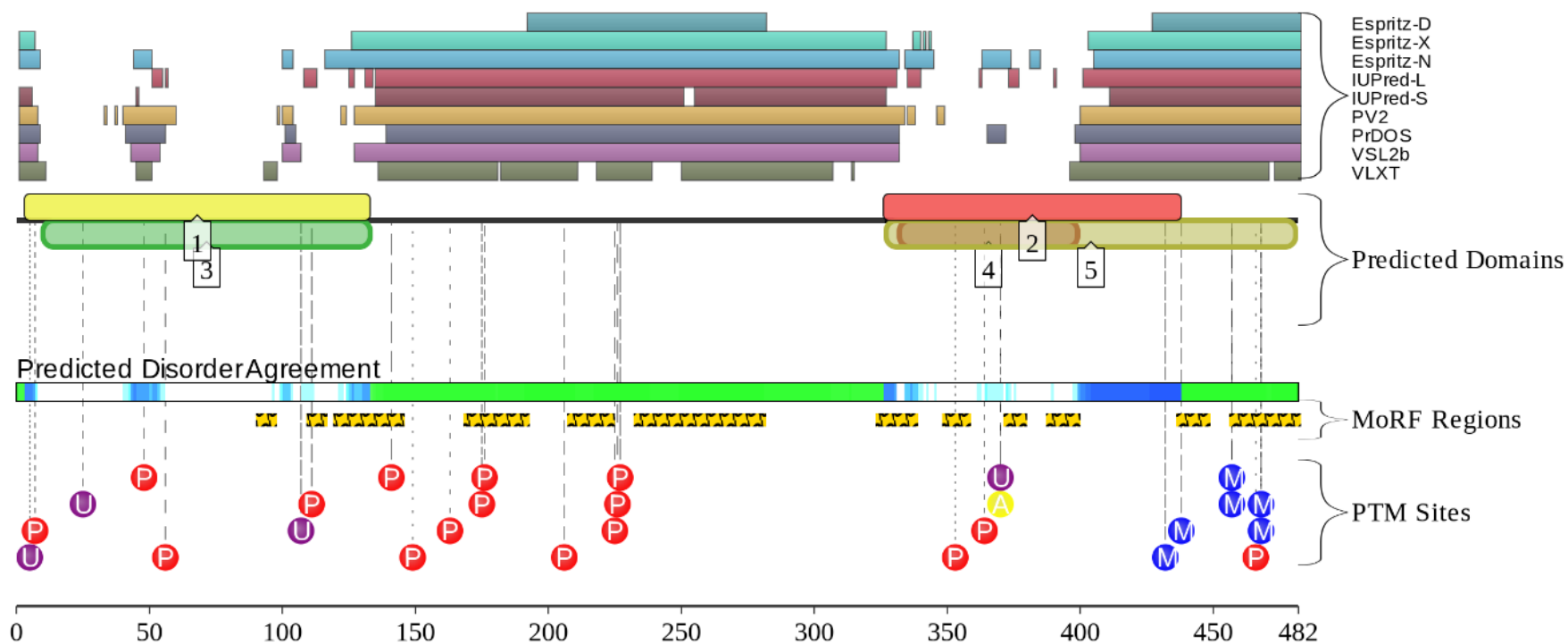
**A**

```
>sp|Q9UN86|G3BP2_HUMAN Ras GTPase-activating protein-binding protein 2 OS=Homo sapiens OX=9606 GN=G3BP2 PE=1 SV=2
MVMEKPSPLLVGREFVRQYYTLLNKAPEYLHRFYGRNSSYVHGGVDASGKPQEAVYGQNDIHHKVLNLFSECHTKIRHVDAAHATLSDGVVVQVMGLLSNSGQPERKFMQTFVLAPEG
SVPNKFYVHNDMFRYEDEVFGDSEPELDEESEDEVEEEEQEERQPSPEPVQENANSGYIEAHPVTNGIEEPLEESSHEPEPEPESETKTEELKPQVEEKNLEELEEKSTTPPPAEPVSL
PQEPPKAFSWASVTSKNLPPSGTVSSGIPPHVKAPVSQPRVEAKPEVQSQPPRVREQRPRERPGFPFPRGPRGRGDMEQNDSDNRRIIRYPDSHQLFVGNLPHDIDENELKEFFMSF
GNVVELRINTKGVGKLPNFGFVVDSEPVQRILIAKPIIMFRGEVRLNVEEKKTRAARERETRGGGDDRRDIRNDRGPGGPRGIVGGGMMRDRDGRGPPPRGGMAQKLGSGRGTGQ
MEGRFTGQRR
```

**B**



c



### Key:

- Predicted SCOP Structure
- ⋯ Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- ⚡ Predicted MoRFs
- ⊙ Curated PTM Site

### Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

### Superfamilies:

- [1] NTF2-like
- [2] RNA-binding domain, RBD

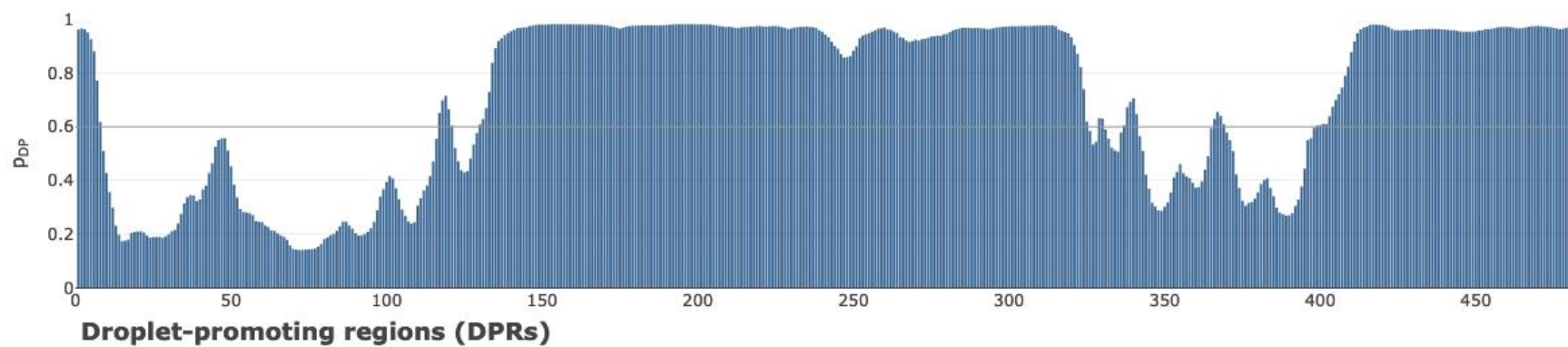
### Pfams:

- [3] Nuclear transport factor 2 (NTF2) domain
- [4] RNA recognition motif. (a.k.a. RRM, RBD, or RNP domain)
- [5] PB002199 (Pfam-B)

D

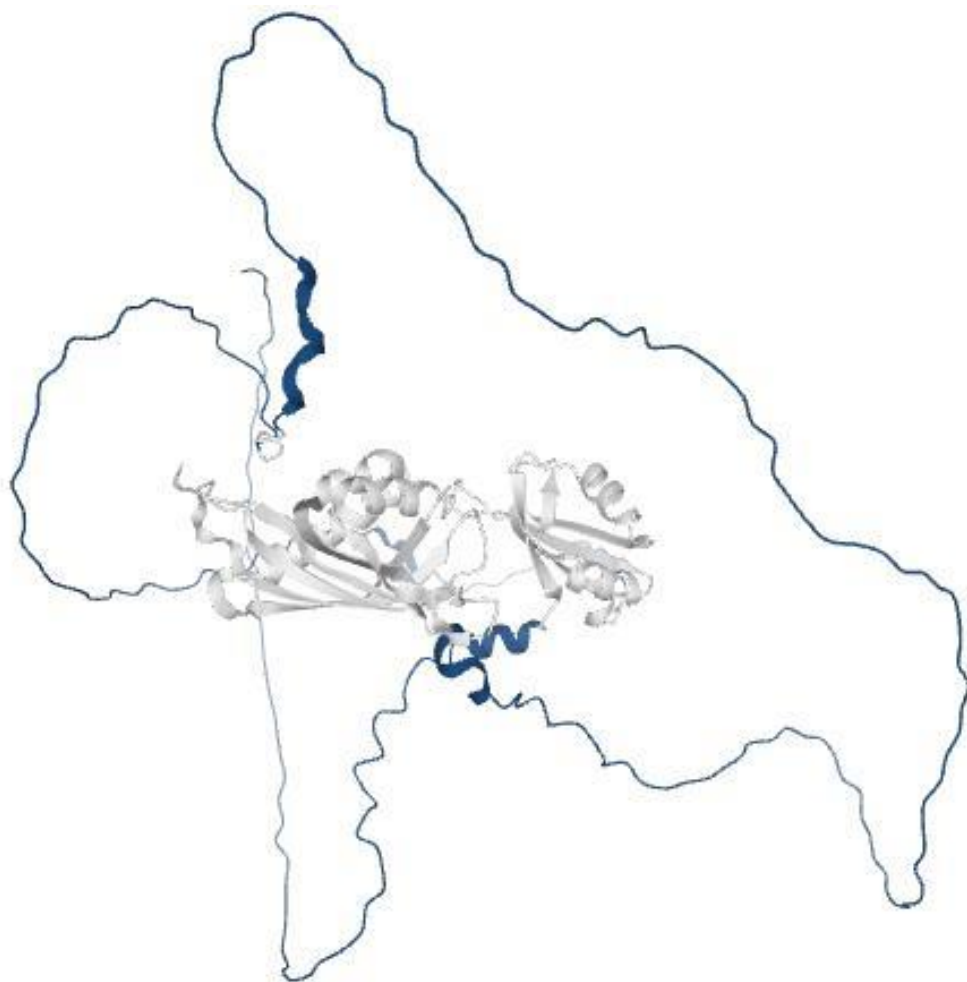
Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.9976$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**



**Aggregation hot-spots**

**E**









minimum required interaction score: medium confidence (0.400)

number of nodes: 106

number of edges: 1045

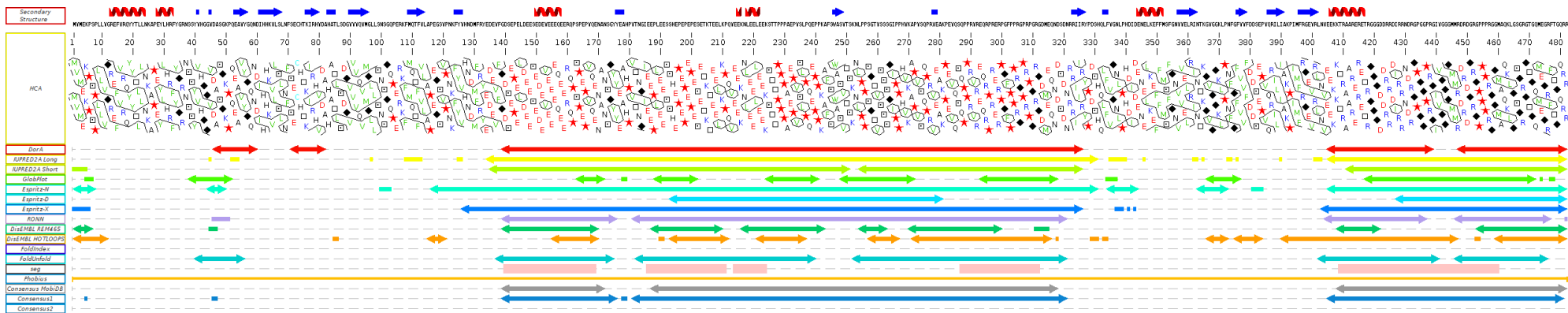
average node degree: 19.7

avg. local clustering coefficient: 0.667

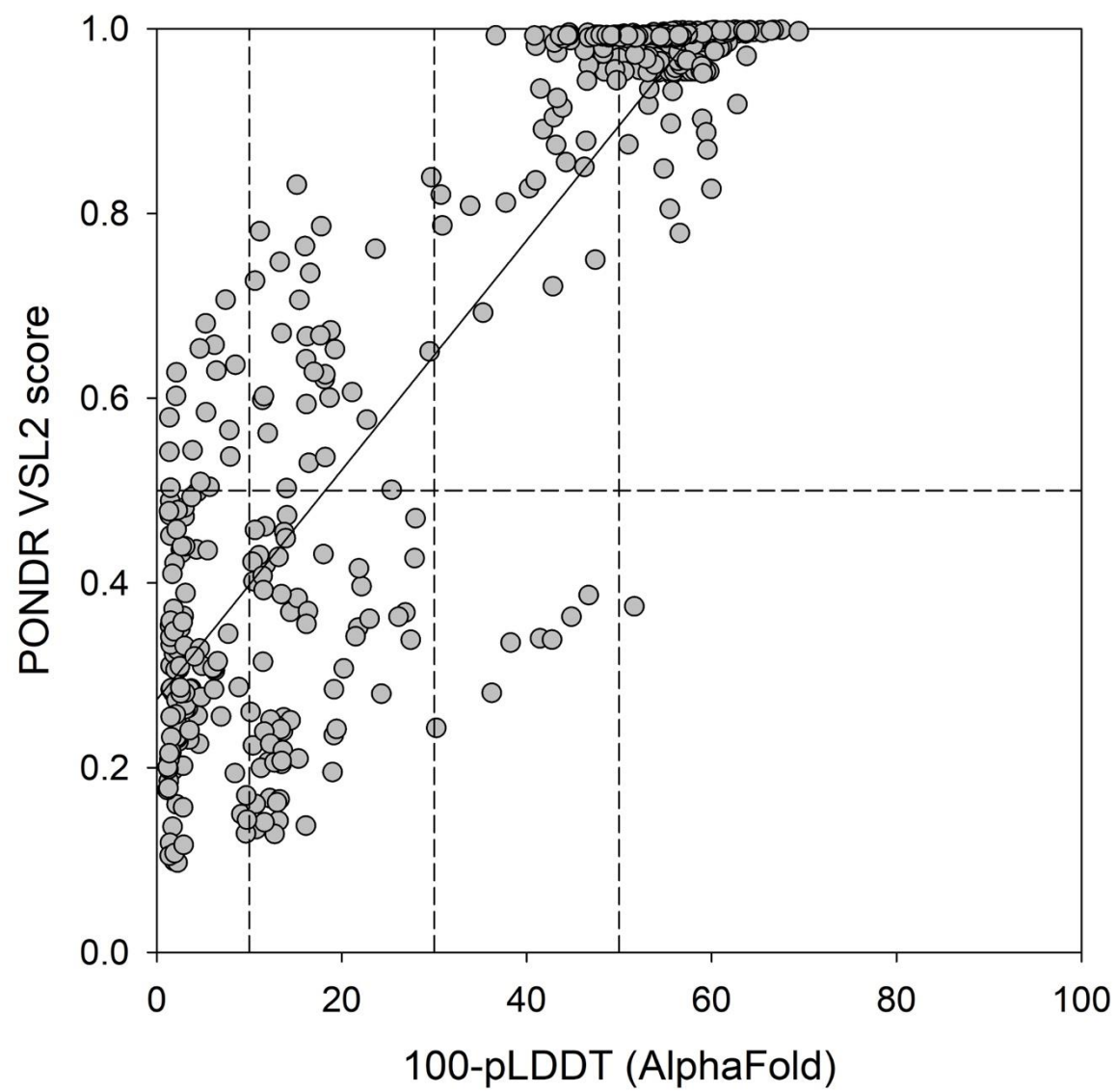
expected number of edges: 281

PPI enrichment p-value:  $< 1.0e-16$

## G



H

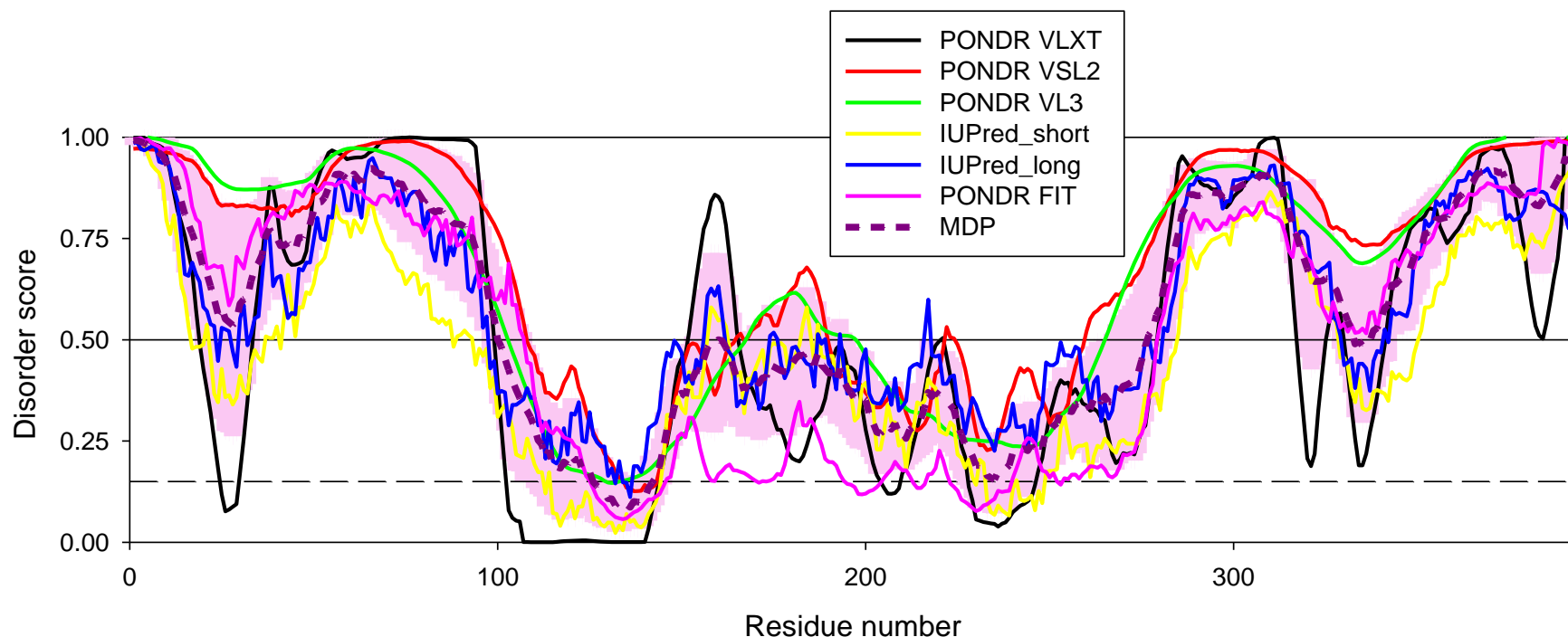


**Supplementary Figure S7.** Functional disorder in cellular tumor antigen p53. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. Note that due to the high p53 interactivity, STRING analysis was conducted using highest confidence of 0.900. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

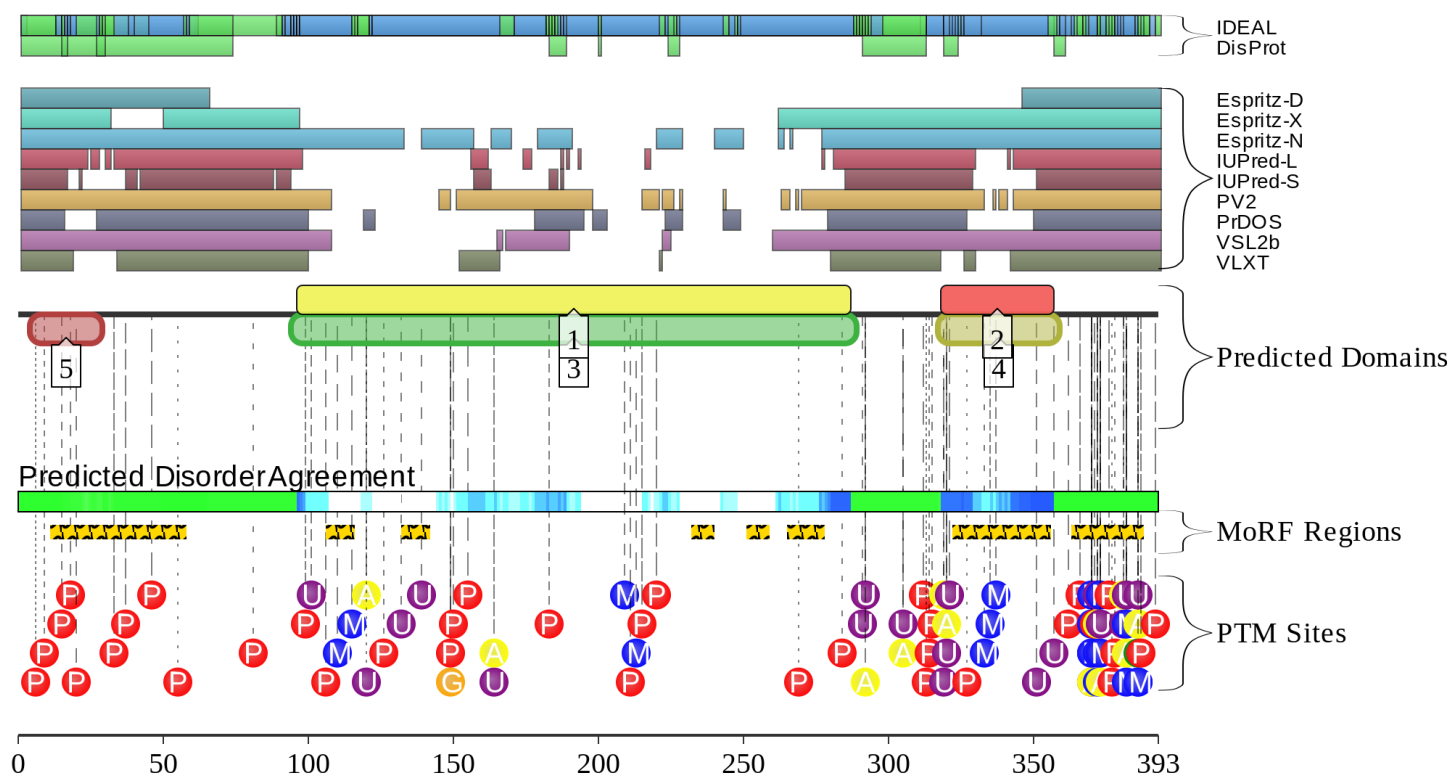
**A**

```
>sp|P04637|P53_HUMAN Cellular tumor antigen p53 OS=Homo sapiens OX=9606 GN=TP53 PE=1 SV=4
MEEPQSDPSVEPPLSQETFSDLWKLLPENNVLSPLPSQAMDDLMLSPDDIEQWFTEDPGPDEAPRMPEAAPVAPAPAAPTPAAPAPAPSWPLSSSVPSQKTYQGSY
GFRLLGLHSGTAKSVTCTYSPALNKMFCQLAKTQCPVQLWVDSTPPPGTRVRAMAIYKQSQHMTVEVVRRCPPHHERCSDSDGLAPPQHLIRVEGNLRVEYLLDDRNTFRH
SVVVPYEPPEVGSDCTTIHYNMCMSSCMGMNRRPILTIITLEDSSGNLLGRNSFEVRVCACPGDRDRTEENLRKKGEPHHELPPGSTKRALPNNTSSSPQPKKK
PLDGEYFTLQIRGRERFEMFRELNEALELKDAQAGKEPGGSRAHSSHLKSKKGQSTSRHKKLMFKTEGPDSD
```

**B**



C



Key:

- Predicted SCOP Structure
- ⋮ Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- ⋈ Predicted MoRFs
- Curated PTM Site

Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

Superfamilies:

- [1] p53-like transcription factors
- [2] p53 tetramerization domain

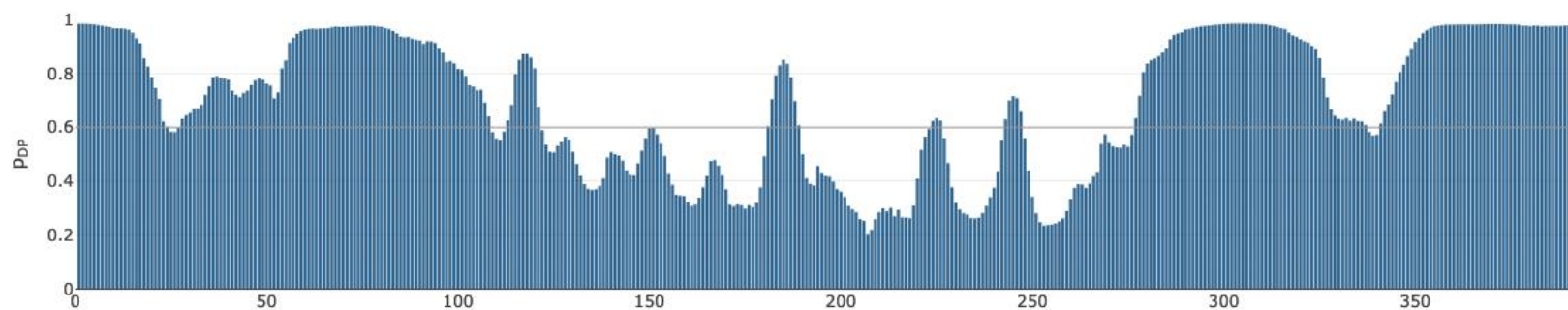
Pfams:

- [3] P53 DNA-binding domain
- [4] P53 tetramerisation motif
- [5] P53 transactivation motif

D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.9848$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**



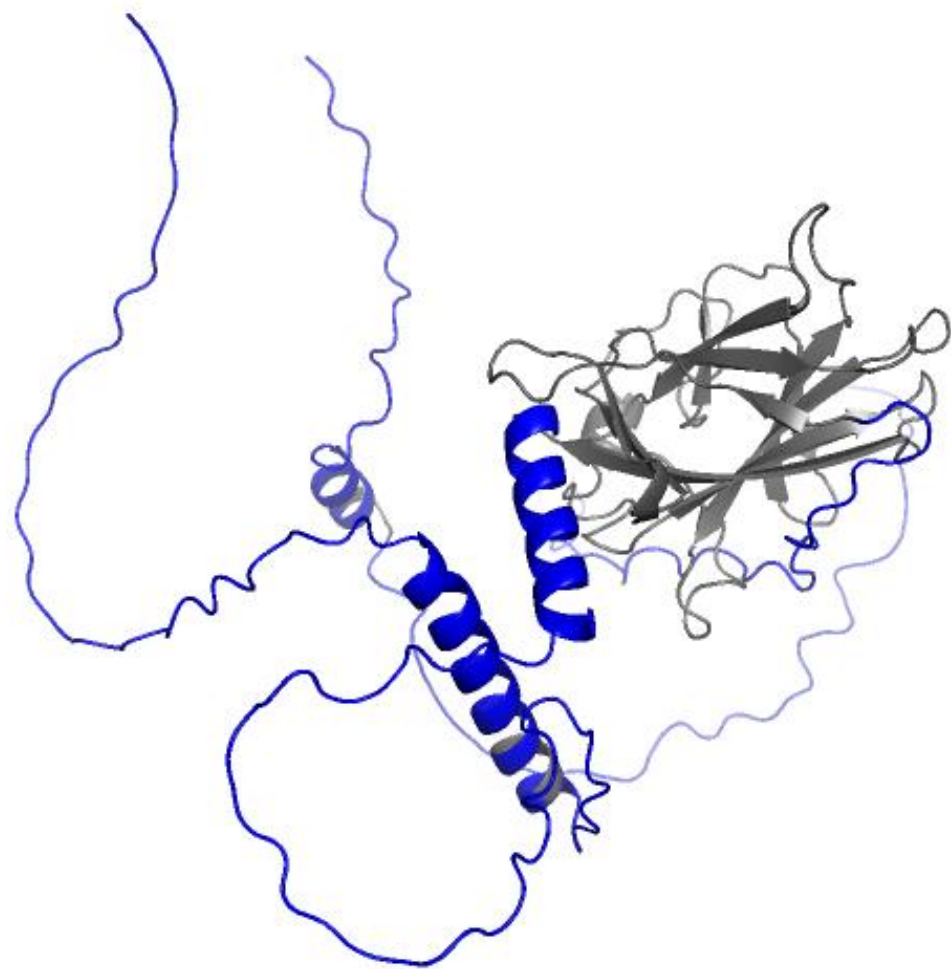
**Droplet-promoting regions (DPRs)**



**Aggregation hot-spots**

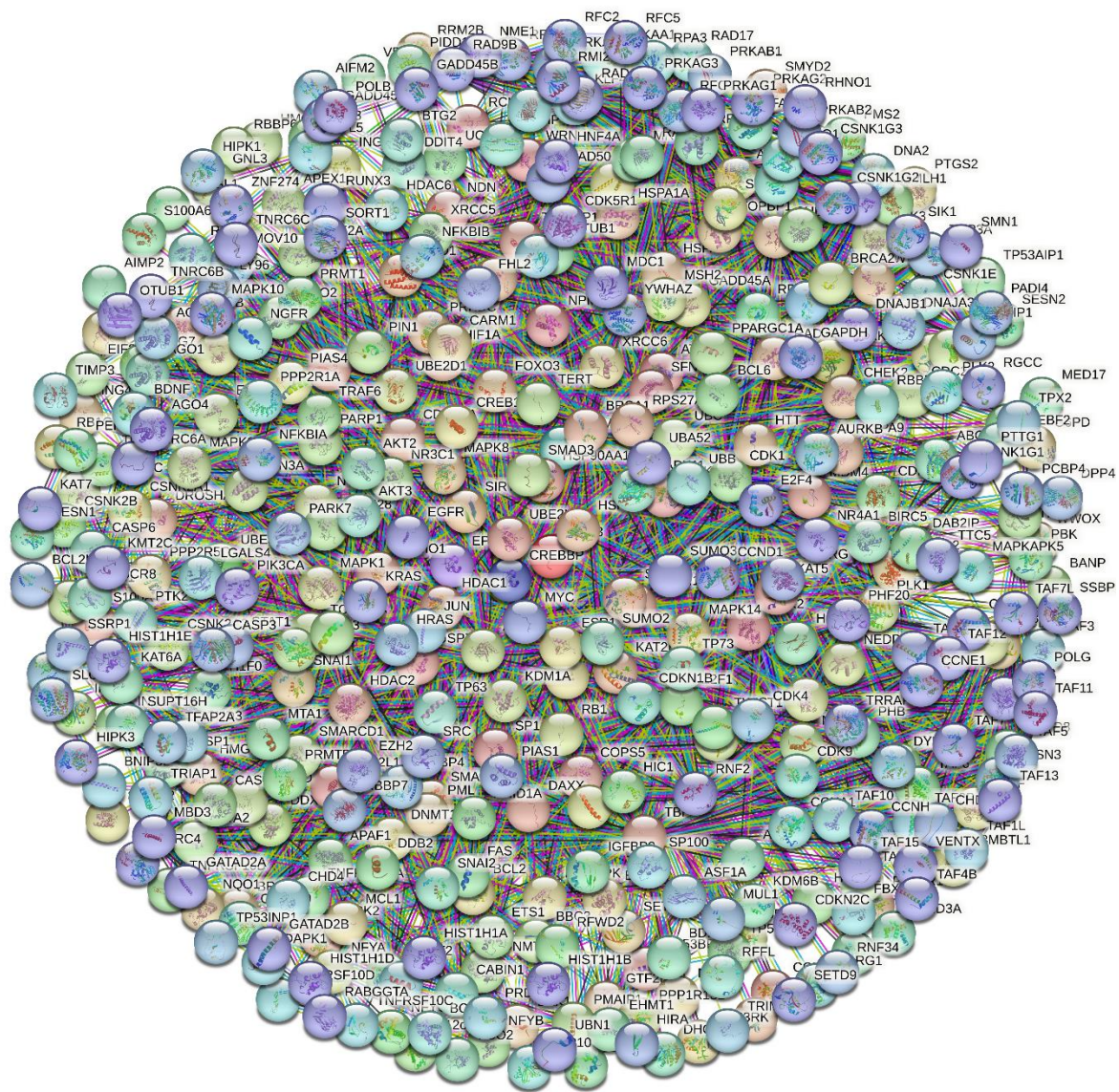


**E**





**F**



minimum required interaction score: highest confidence (0.900)

number of nodes: 427

number of edges: 3677

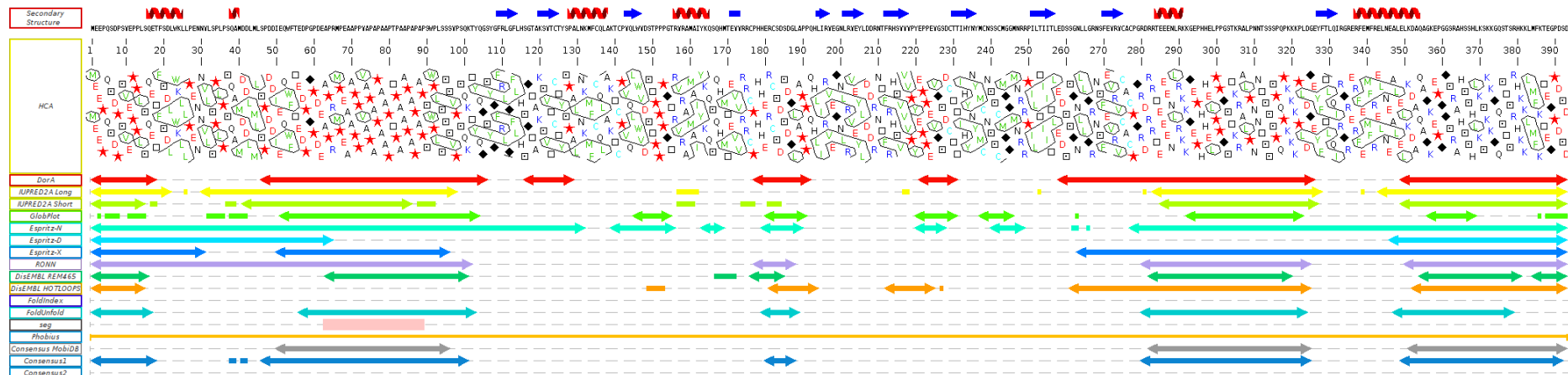
average node degree: 17.2

avg. local clustering coefficient: 0.62

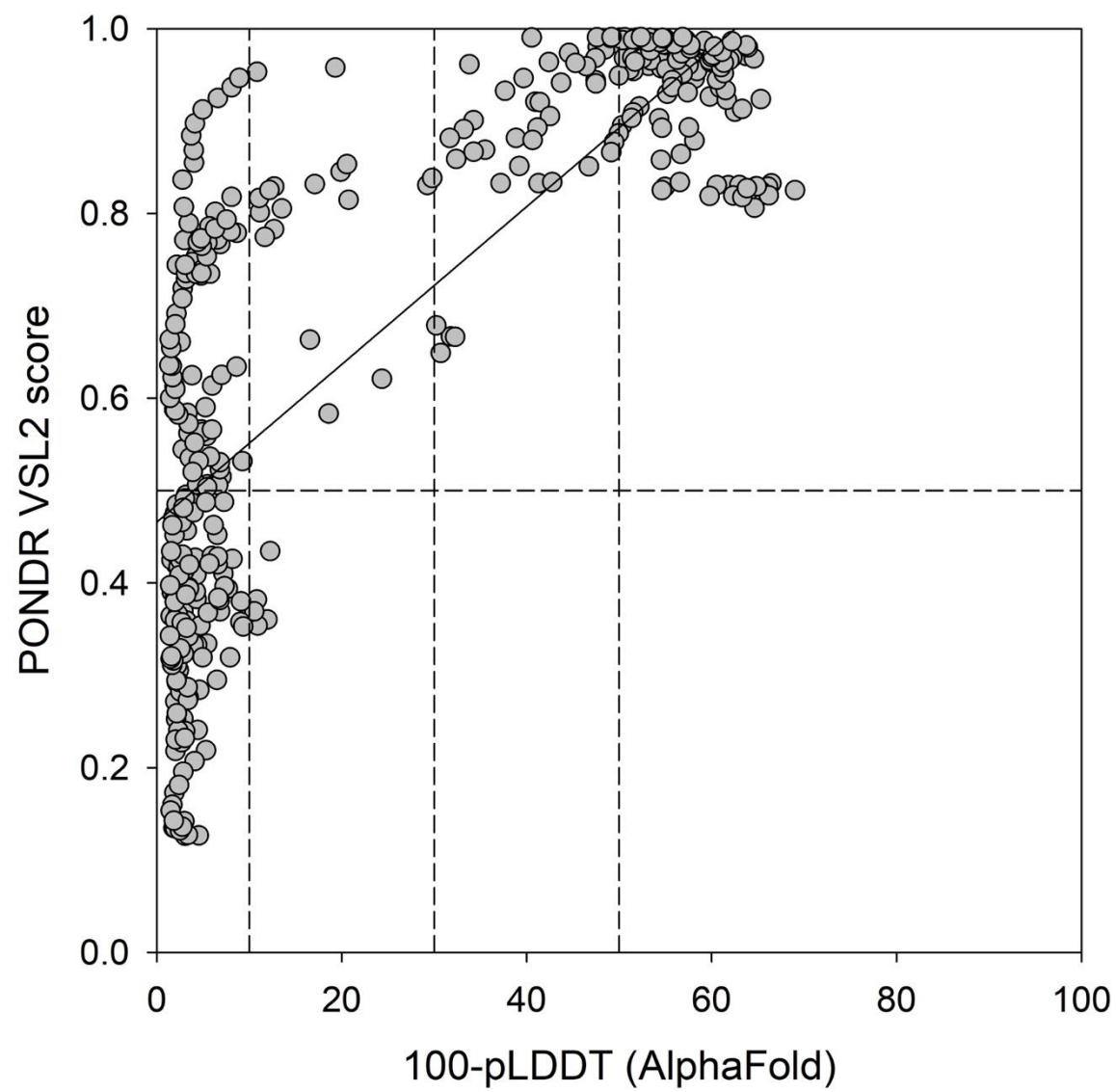
expected number of edges: 1903

PPI enrichment p-value:  $< 1.0e-16$

G



H

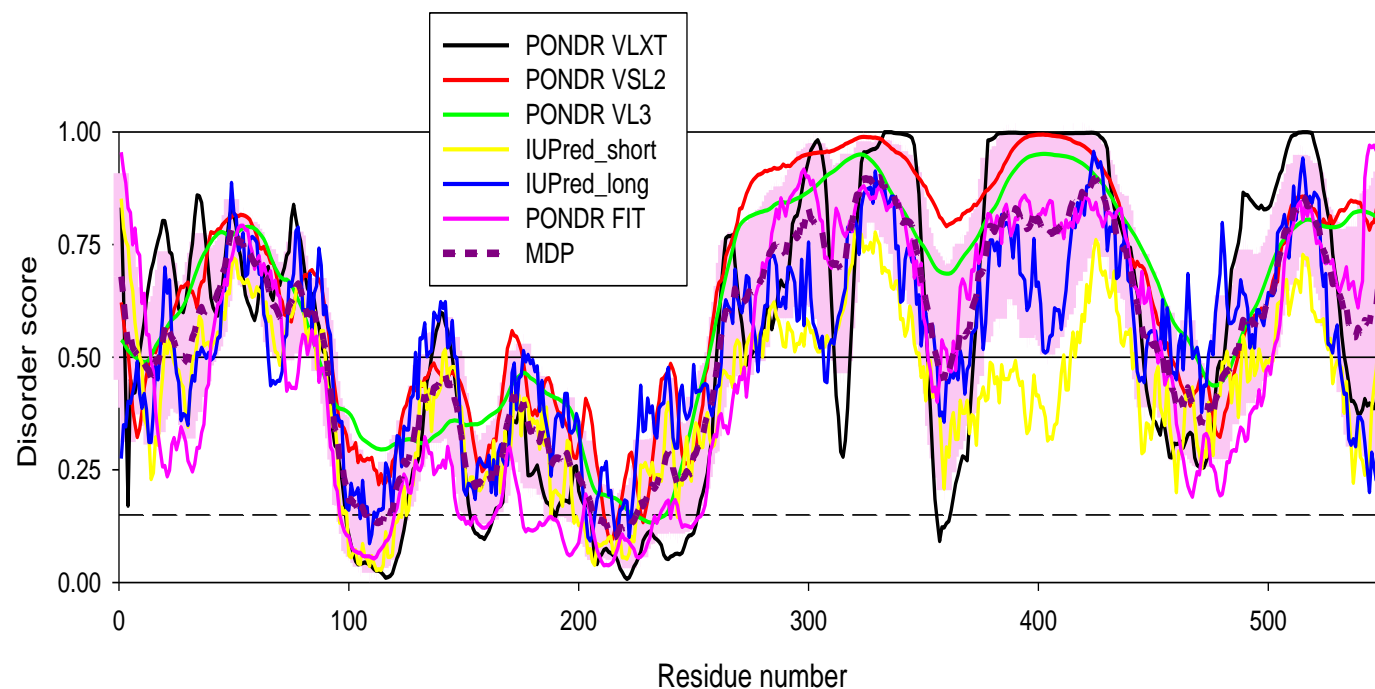


**Supplementary Figure S8.** Functional disorder in transcription factor p65. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

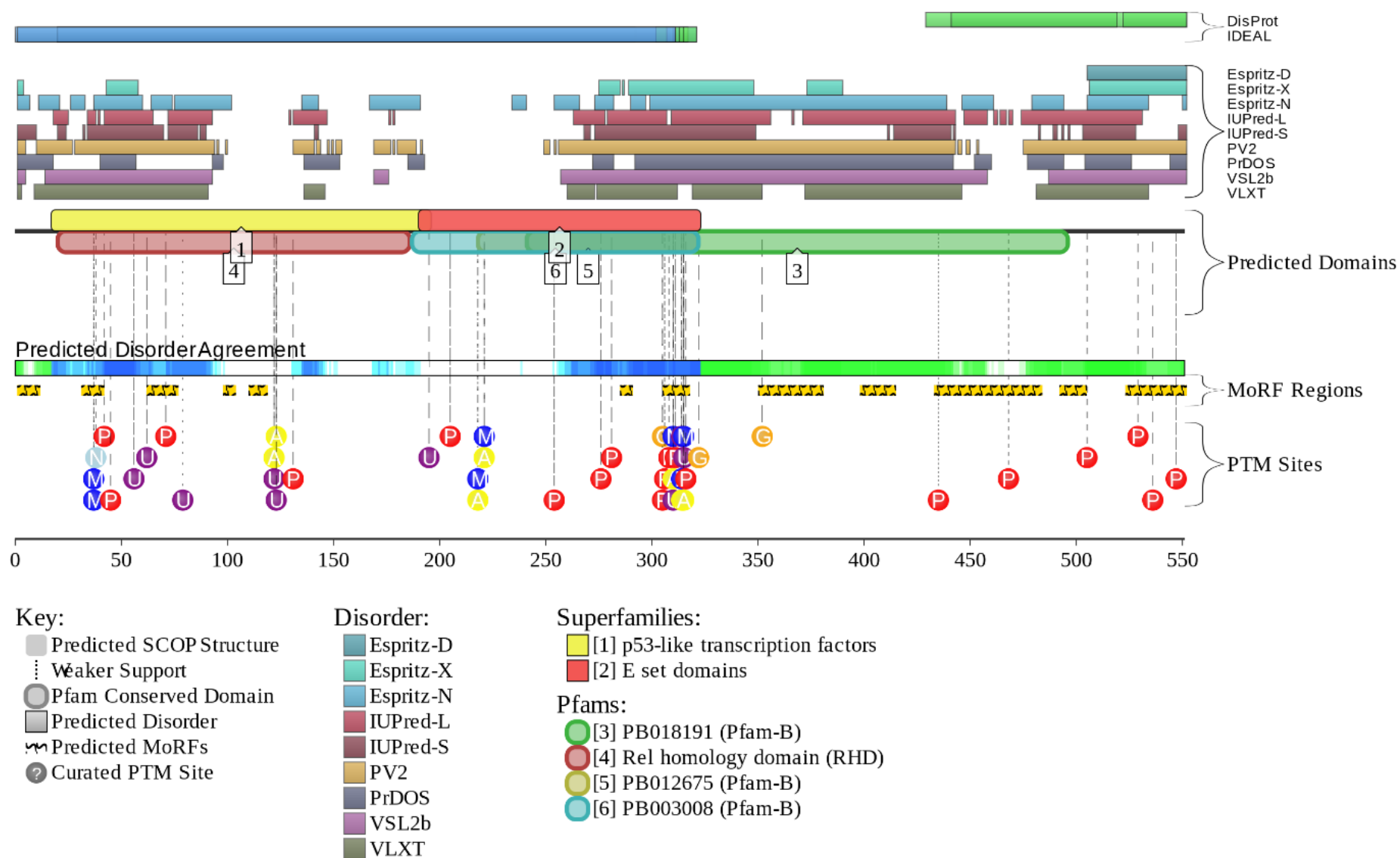
**A**

```
>sp|Q04206|TF65_HUMAN Transcription factor p65 OS=Homo sapiens OX=9606 GN=RELA PE=1 SV=2
MDELFLIFPAEPAQASGPYVEIIEQPKQGRMFRYKCEGRSAGSIPGERSTDTTKTHPTIKINGYTGP GTVRISLVTKDPPHRPHPHELVGKDCRDGFYEAELCPDRCIHSFQNLGI
QCVKKRDLEQAISQRIQTNNNPFQVPIEEQRGDYDLNAVRLCFQVTVRDP SGRPLRLPPVLSHPIFDNRAPNTAELKICRVNRNSGSLGGDEIFLLCDKVQKEDIEVYFTGPGWEAR
GSFSQADVHRQVAIVFRTPPYADPSLQAPVRVSMQLRRPSDRELSEPMEFQYLPD TDDRHRIEEKRKRTYETFKSIMKKS PFSGPTDPRPPPRRIAVPSRSSASVPKPAPQYPFTSS
LSTINYDEFPTMVFP SGQISQASALAPAPPQVLPQAPAPAPAPAMVSALAQA PAVPVVLAPGPPQAVAPPAPKPTQAGEGTLSEALLQLQFDDDELGALLGNSTDP AVFTDLASVDNS
EFQQLLNQGIPVAPHTTEPMLMEYPEAITRLVTGAQRPPDPAPAPLGA PGLPNGLLSGDEDFSSIADMDFSALLSQISS
```

**B**



c

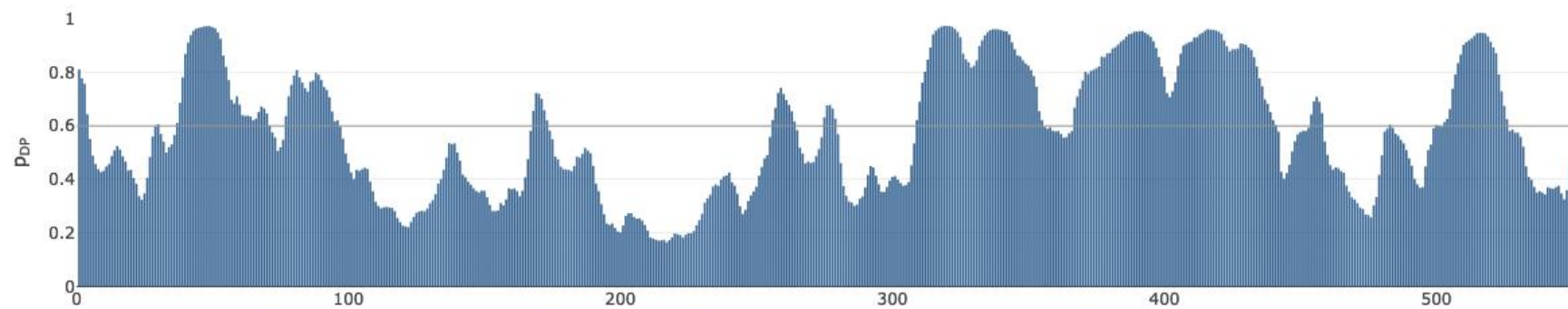




D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.9487$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**



**Droplet-promoting regions (DPRs)**

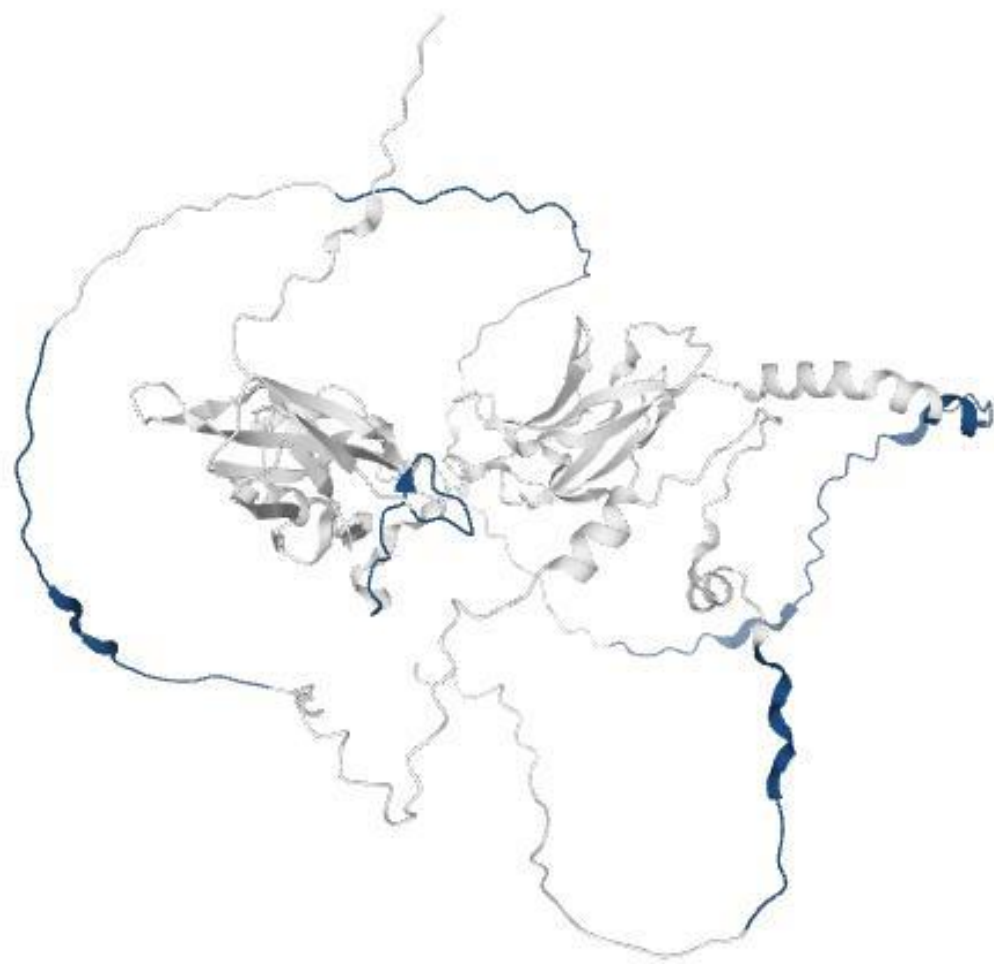


**Aggregation hot-spots**





**E**





minimum required interaction score: high confidence (0.700)

number of nodes: 323

number of edges: 5565

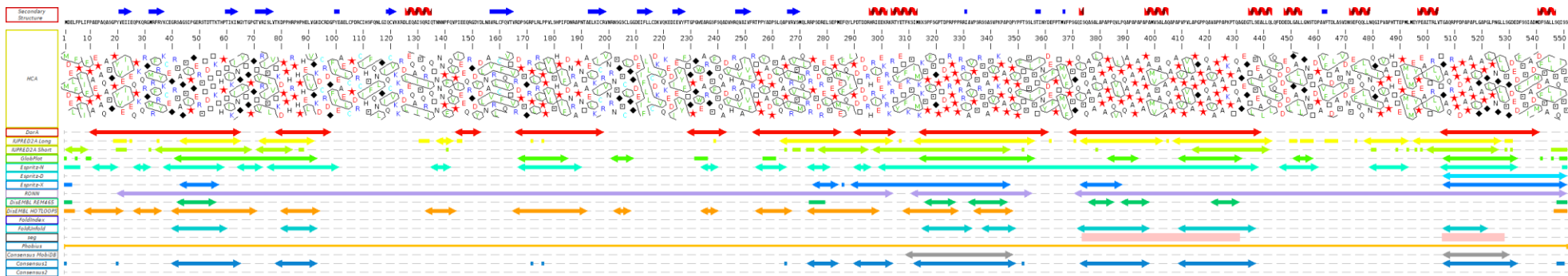
average node degree: 34.5

avg. local clustering coefficient: 0.661

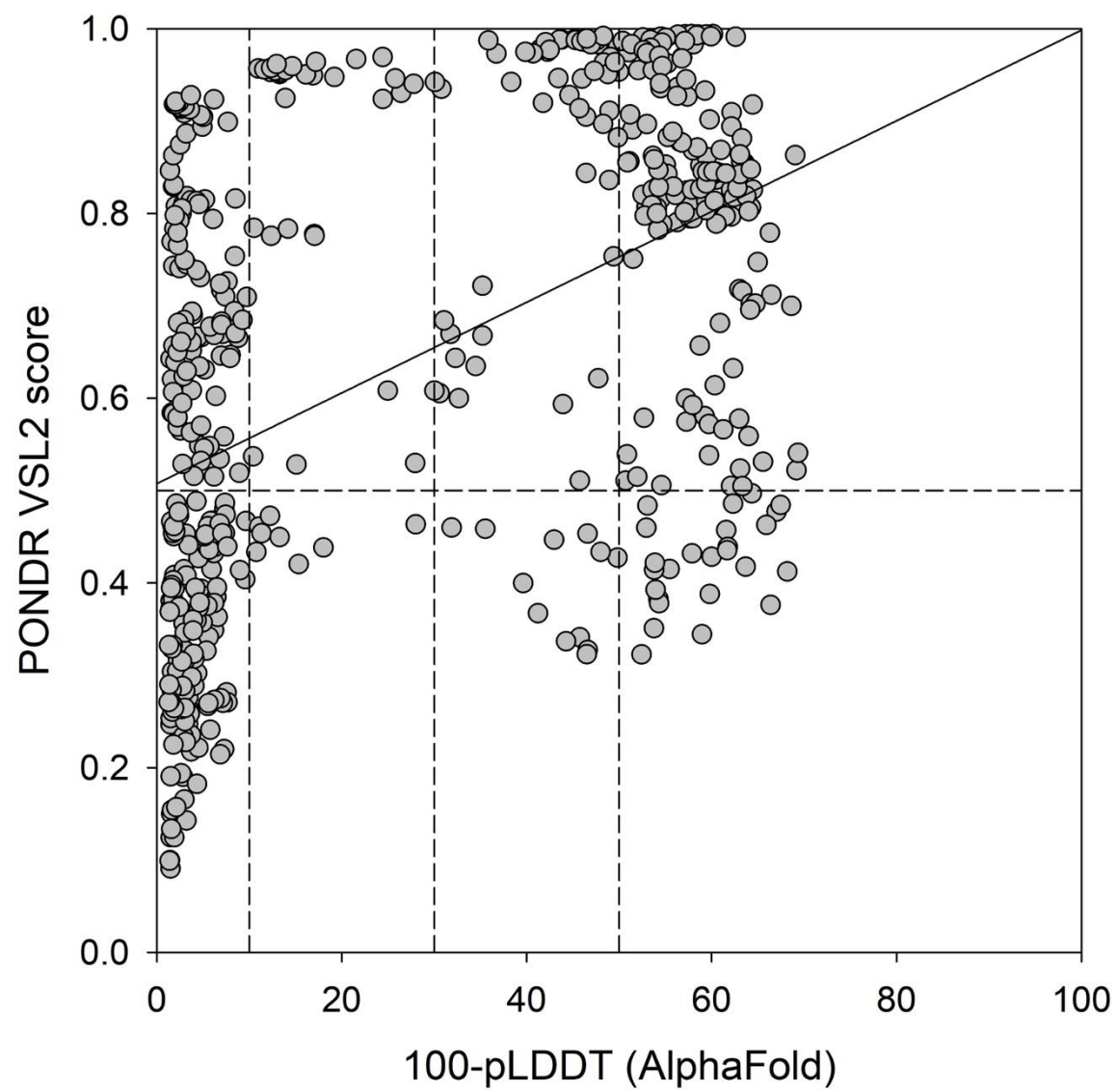
expected number of edges: 2037

PPI enrichment p-value:  $< 1.0e-16$

**G**



H

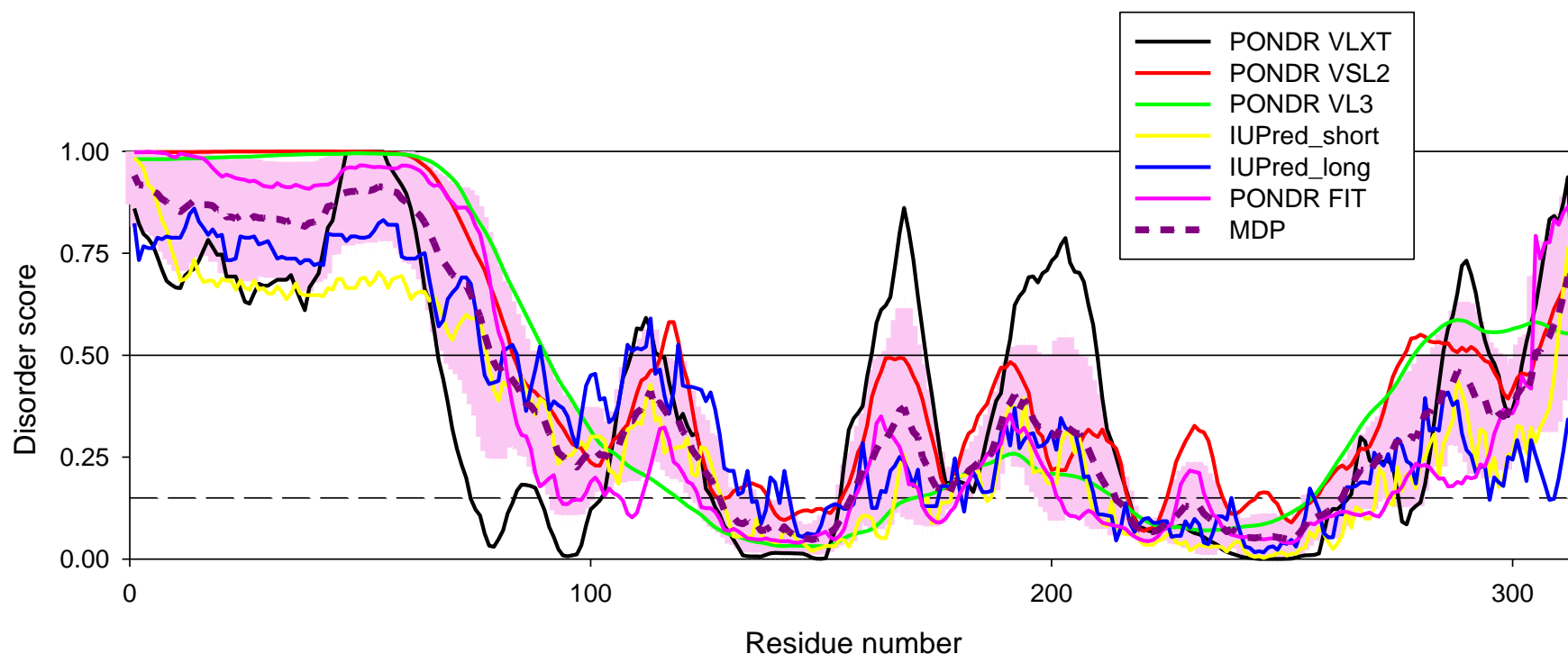


**Supplementary Figure S9.** Functional disorder in fibrillarin 2. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>tr|B7VCB9|B7VCB9_NICBE Fibrillarin 2 OS=Nicotiana benthamiana OX=4100 GN=fib2 PE=2 SV=1
MVAPTRGRGGGGFRGGRGDGGGRGGRGGRGGFGGGRGGGGSAMKRGGGRGGGGRGGGGRGGGRGGGFKGGNKVVVEPHRHGGVFIAGKEDALCTKNLVPGEAVYNEKRISVQNE
DGTKVEYRVWNPFRSKLAAAVLGGVDDIWIKPGAKVLYLGAASGTTVSHVSDLVGPGGVVYAVEFSHRSGRDLVNMAKKRTNVIPIEDARHPAKYRMLVGMVDVIFSDVAQPDQARILA
LNASYFLKAGGHFVISIKANCIDSTVPAAEVFAQEVEKKLQAEQFKPMEQVTLEPFERDHACVVGAYRVPPKKQKAAA
```

**B**



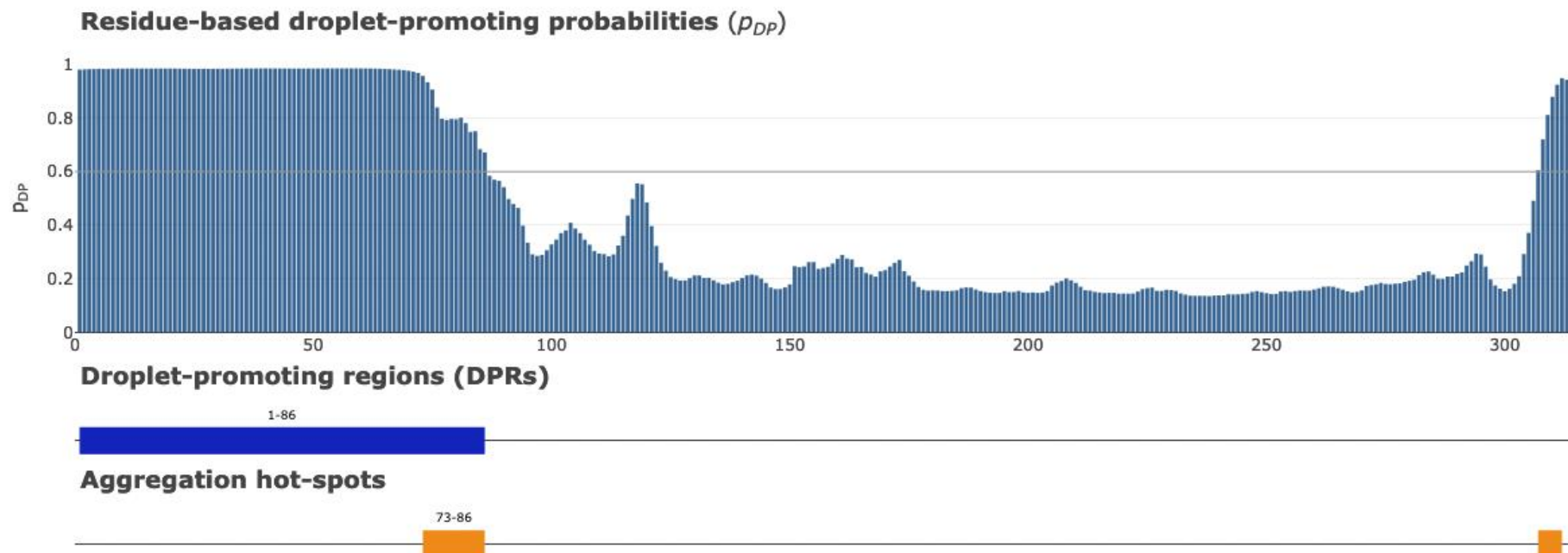
**C**

D<sup>2</sup>P<sup>2</sup> does not have data for Fibrillarin 2 and functional disorder profile cannot be generated



**D**

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.3248$



**E**

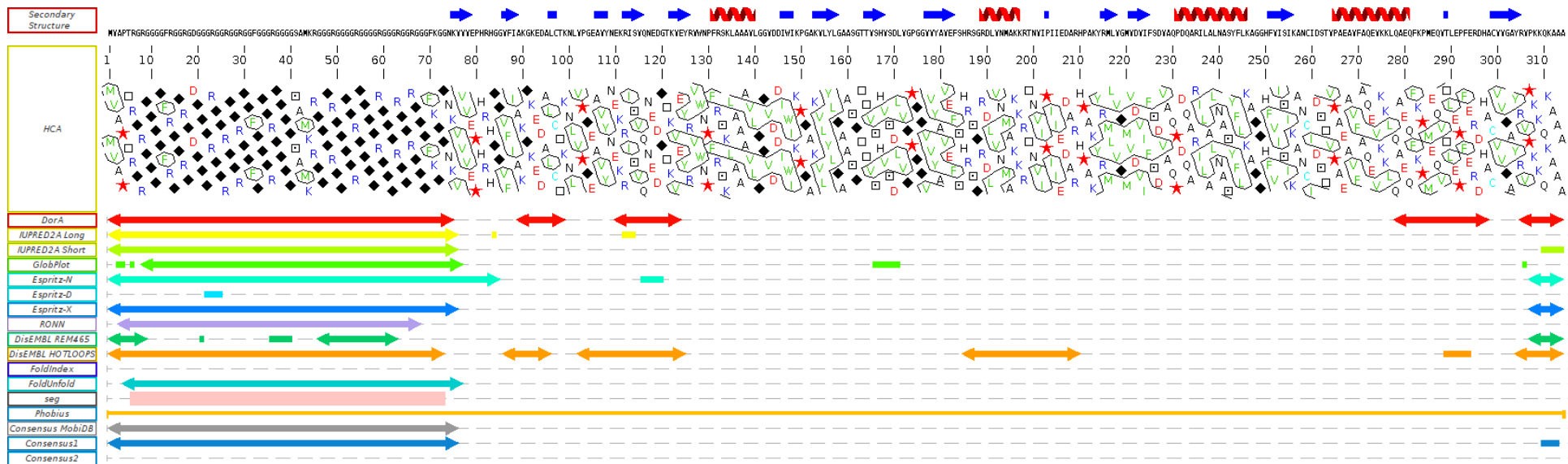
There is no AlphaFold modeled structure for Fibrillarin 2

**F**

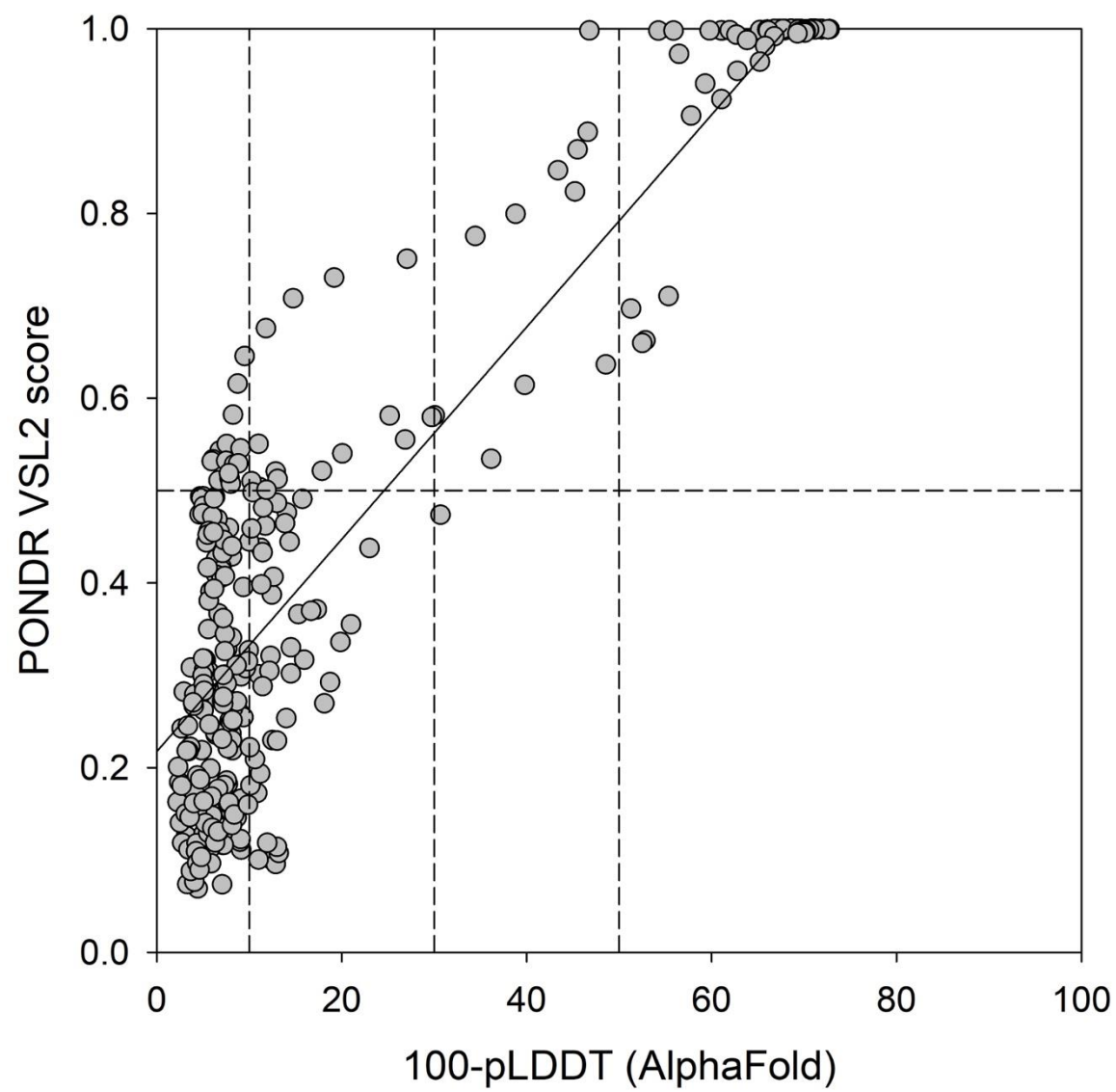
STRING-based protein-protein interaction network centered on Fibrillarin 2 is not available



**G**



H

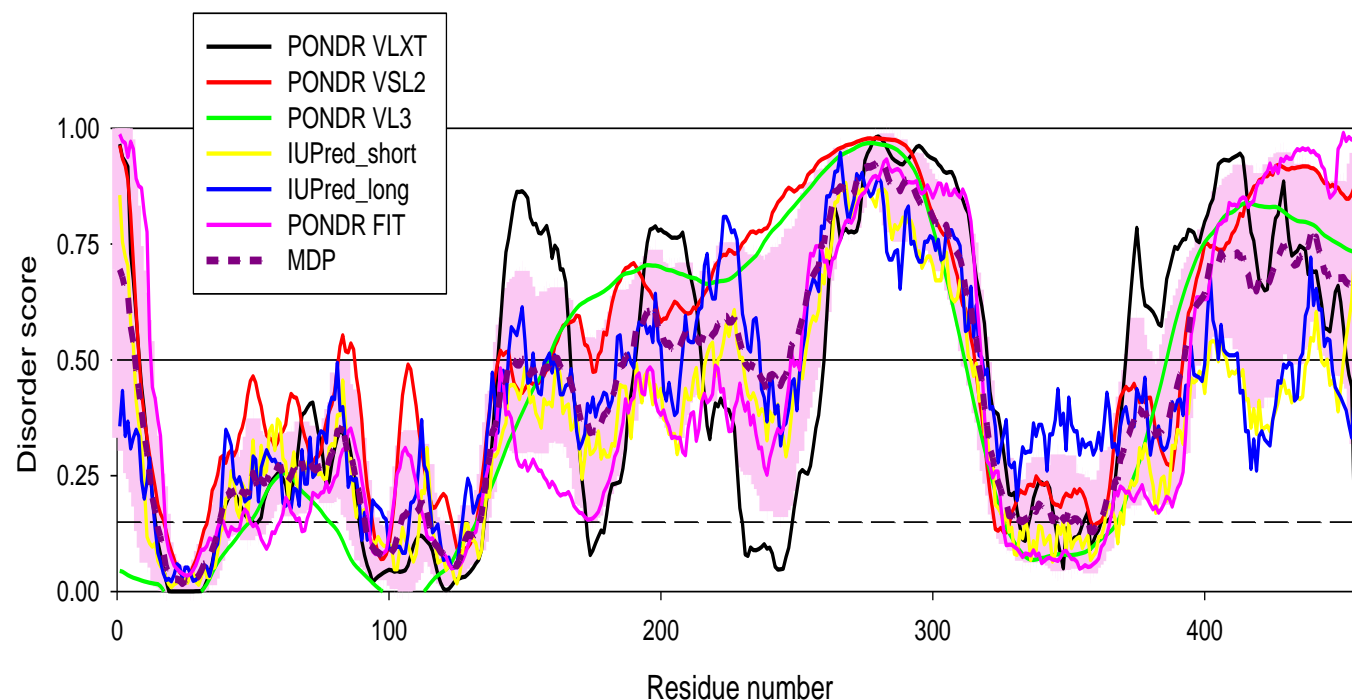


**Supplementary Figure S10.** Functional disorder in nuclear transport factor 2 (NTF2) family protein with RNA binding (RRM-RBD-RNP motifs) domain-containing protein. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

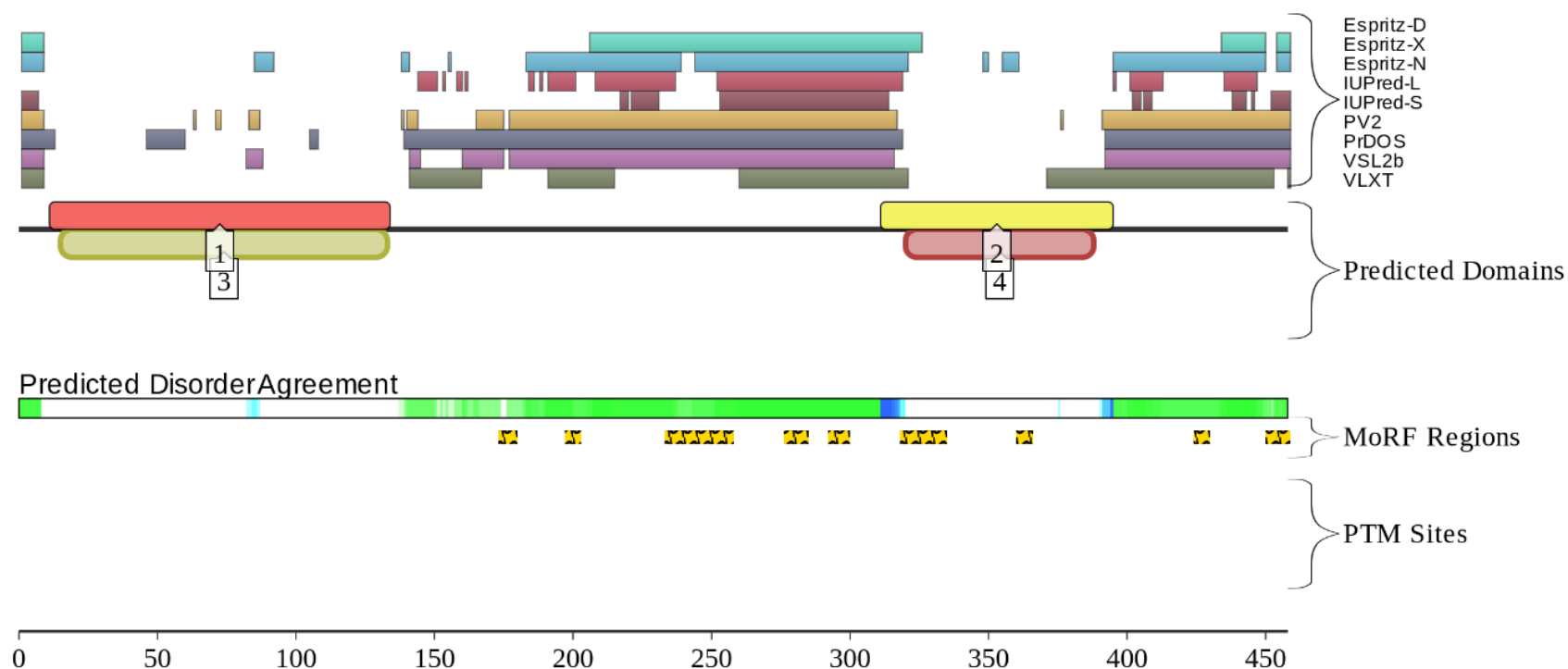
**A**

```
>tr|Q84JH2|Q84JH2_ARATH Nuclear transport factor 2 (NTF2) family protein with RNA binding (RRM-RBD-RNP motifs) domain-
containing protein OS=Arabidopsis thaliana OX=3702 GN=At5g48650 PE=1 SV=1
MDSTAATKRVVDPLTVGSAFVNQYYYIFCNMPEHLPRFYQEISRVRVGQDGVMRDFSTFQGISEELKRLTYGDCNSAEITSYDTQESHNGGFLLFVTGYFTLNERSRRKFTQTFFLA
PQEKGFVVLNDILRFVNDDAKDNVPETIDGEVVSIGINSTTPTIINGMKGSEQAACVSVNPVCKEVSKPLDNENAKDNVLVPEIANEVARTEITCKEVADDSQKNYDPDDGLADAPKKS
YASVLKVTCKDKFGVPAVSLPSPKKIPKDKQEHQAPSDPSTGQILKDQGGQASSDPSQVIESDVTSESVDASENGHNQEAVAEGTSIYVRHLFPNANIDMLEAEFKQFGAITNGGIQVIN
QRGLGYPYGFVEFEEADAHRAIEASPVKIGGLRAFVEEKLSTSRGKRGNGNVGYGNRNVGVGMGRGRGSYGYGYDYRRGGRGPGGGGRSFNRRGNEYVASINSY
```

**B**



c



### Key:

- Predicted SCOP Structure
- ⋮ Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- ⋈ Predicted MoRFs
- Curated PTM Site

### Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

### Superfamilies:

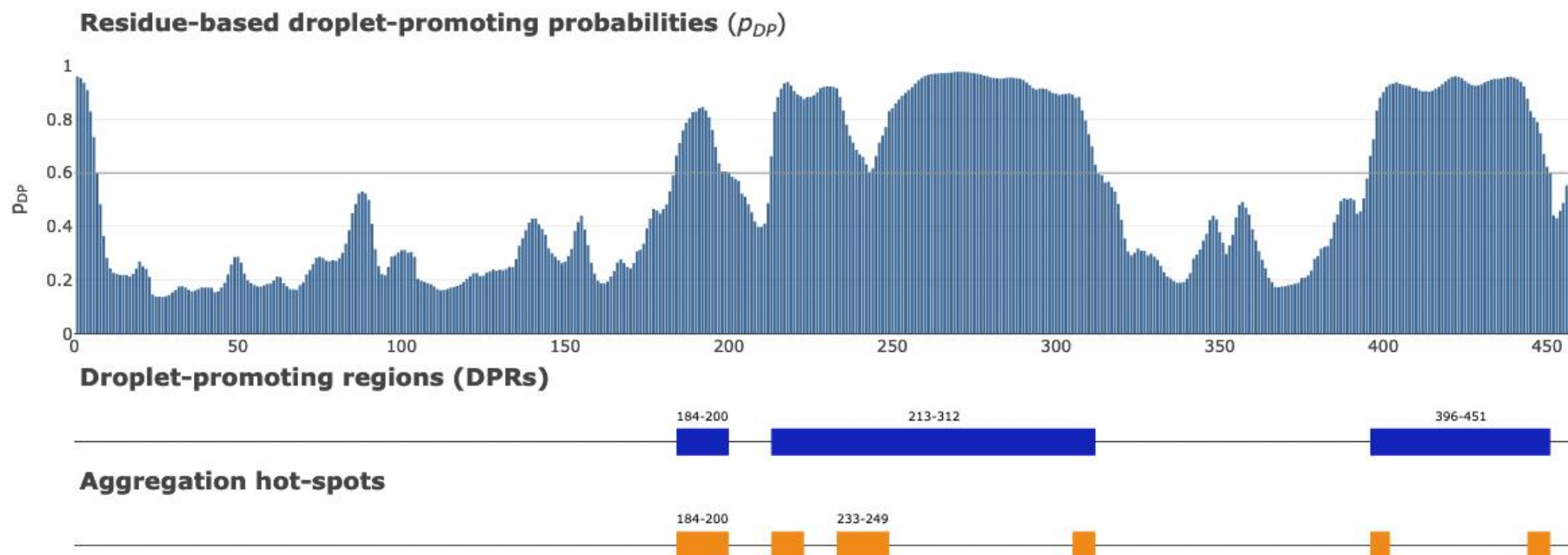
- [1] NTF2-like
- [2] RNA-binding domain, RBD

### Pfams:

- [3] Nuclear transport factor 2 (NTF2) domain
- [4] RNA recognition motif. (a.k.a. RRM, RBD, or RNP domain)

**D**

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.7408$



**E**

There is no AlphaFold2-generated structure for this protein at FuzDrop





minimum required interaction score: low confidence (0.150)

number of nodes: 411

number of edges: 27495

average node degree: 134

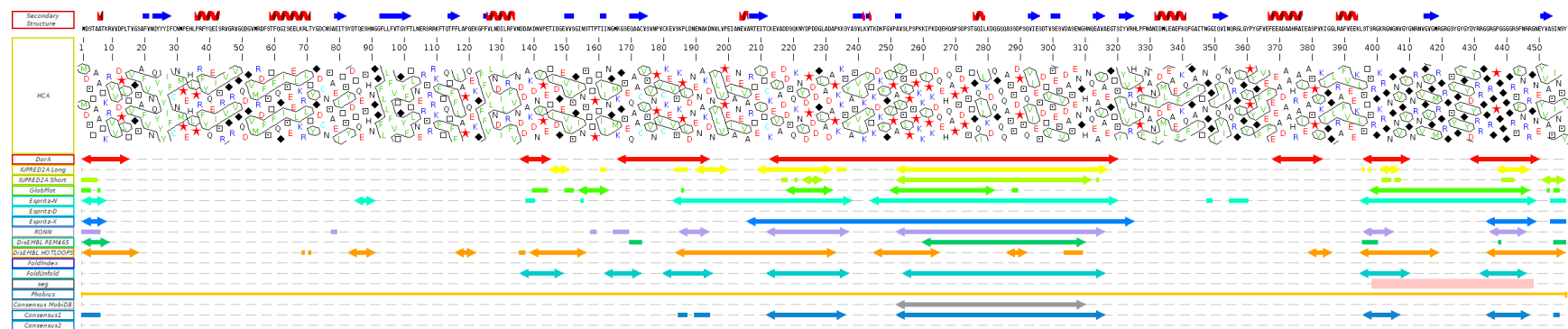
avg. local clustering coefficient: 0.611

expected number of edges: 13087

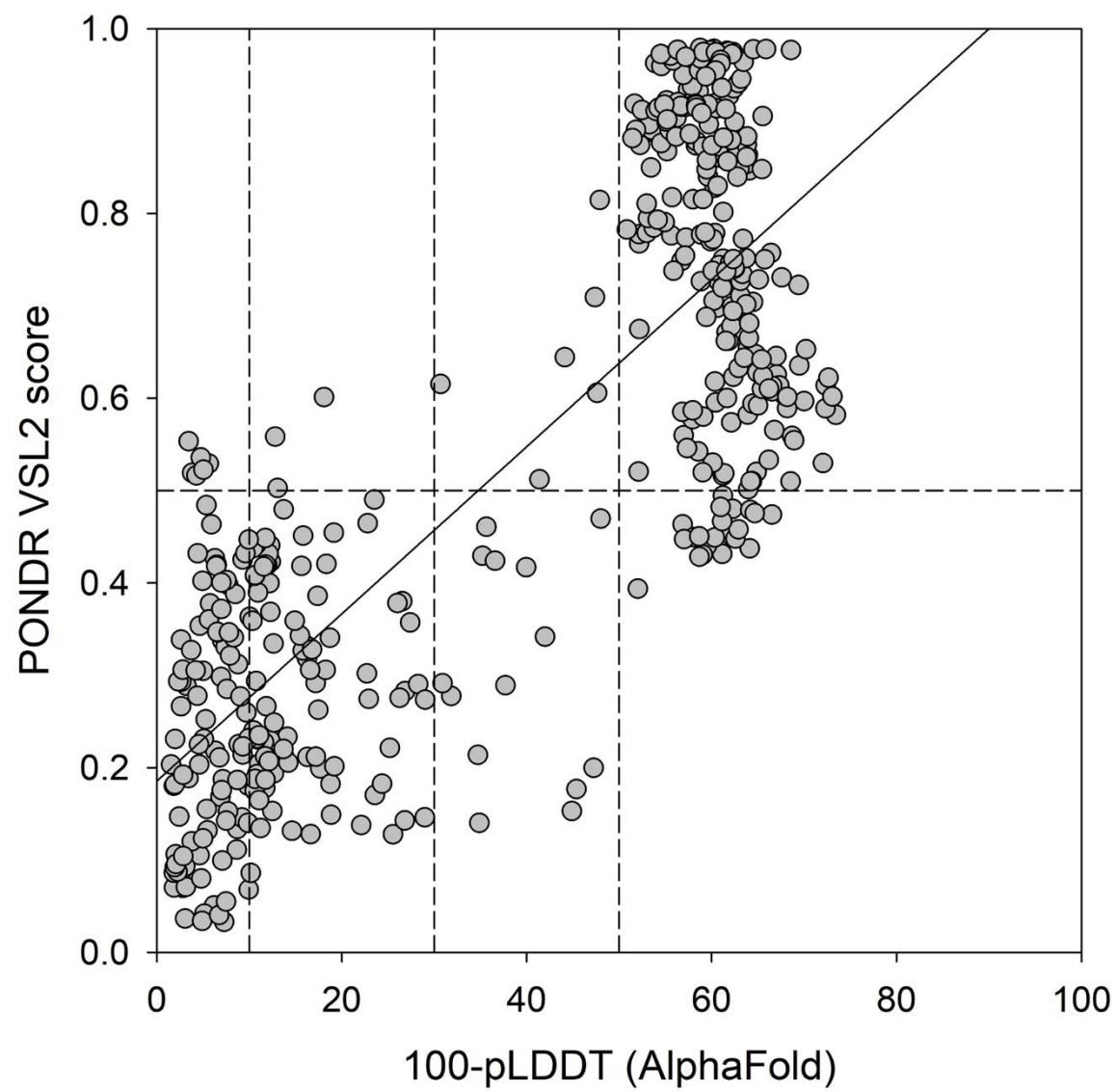
PPI enrichment p-value:  $< 1.0e-16$



G



H

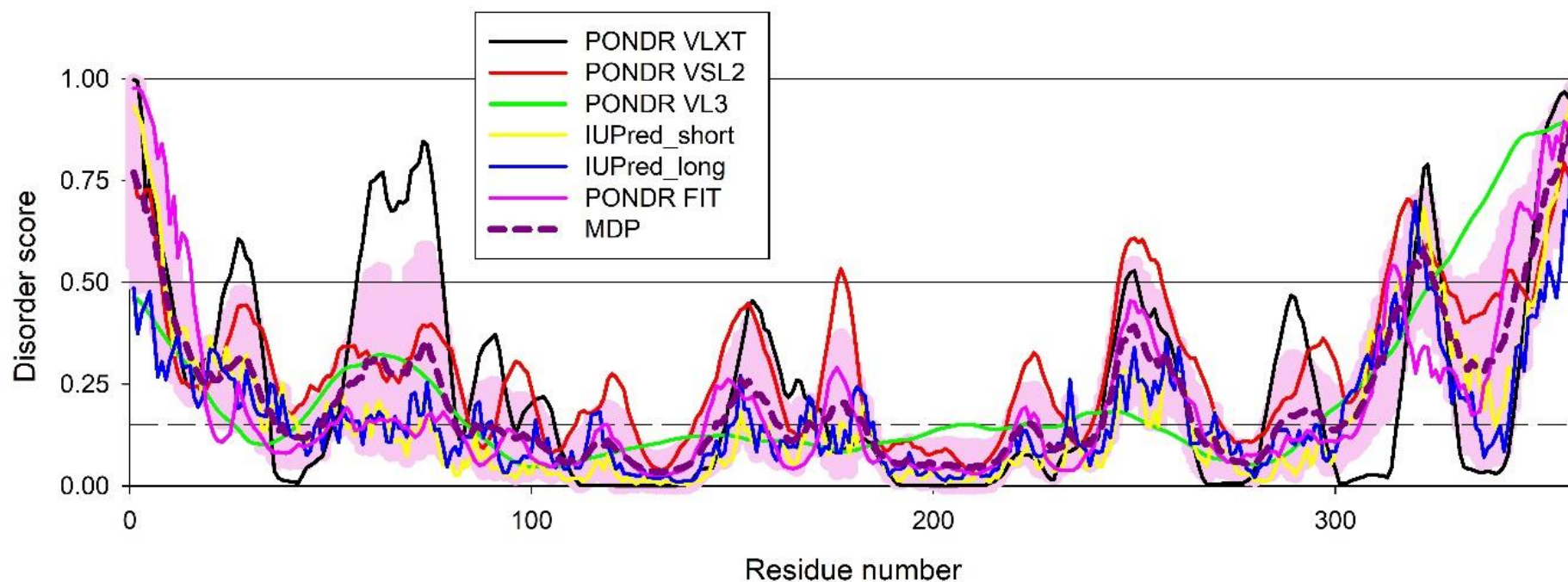


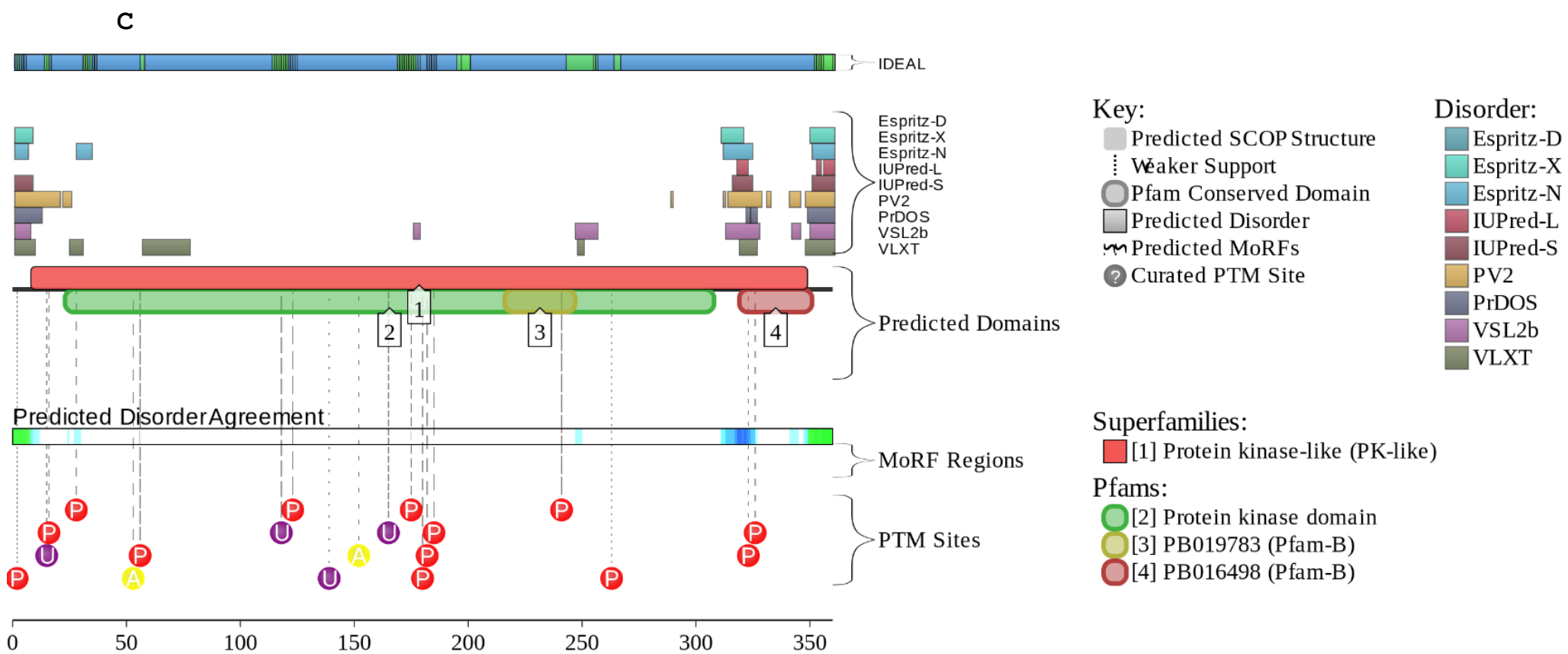
**Supplementary Figure S11.** Functional disorder in mitogen-activated protein kinase 14. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>sp|Q16539|MK14_HUMAN Mitogen-activated protein kinase 14 OS=Homo sapiens OX=9606 GN=MAPK14 PE=1 SV=3
MSQERPTFYRQELNKTIEWPERYQNLSPVGSGAYGSVCAAFDTKTGLRVAVKKLSRPFQSIHAKRTYRELRLKHKHENVIGLLDVFTPARSLEEFNDVYLVTHLMGADLNNIVK
CQKLTDDHVQFLIYQILRGLKYIHSADIHRDLKPSNLAVNEDCELKILDFGLARHTDDEMTGYVATRWRAP EIMLNWMHYNQTVDIWSVGCIMAELLTGRTLFPGTDHIDQLKLIL
RLVGTPGAELLKKISSESARNYIQSLTQMPKMN FANVFIGANPLAVDLLEKMLVLDSDKRITAAQALAHAYFAQYHDPDDEPVADPYDQSFESRDLLIDEWKSLTYDEVISFVPPPLD
QEEMES
```

**B**

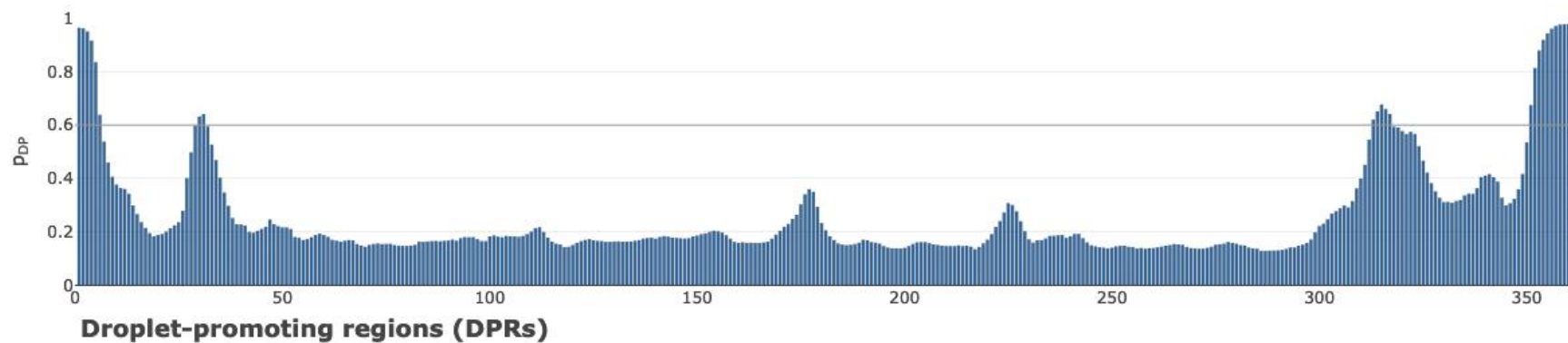




**D**

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.1119$

**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**

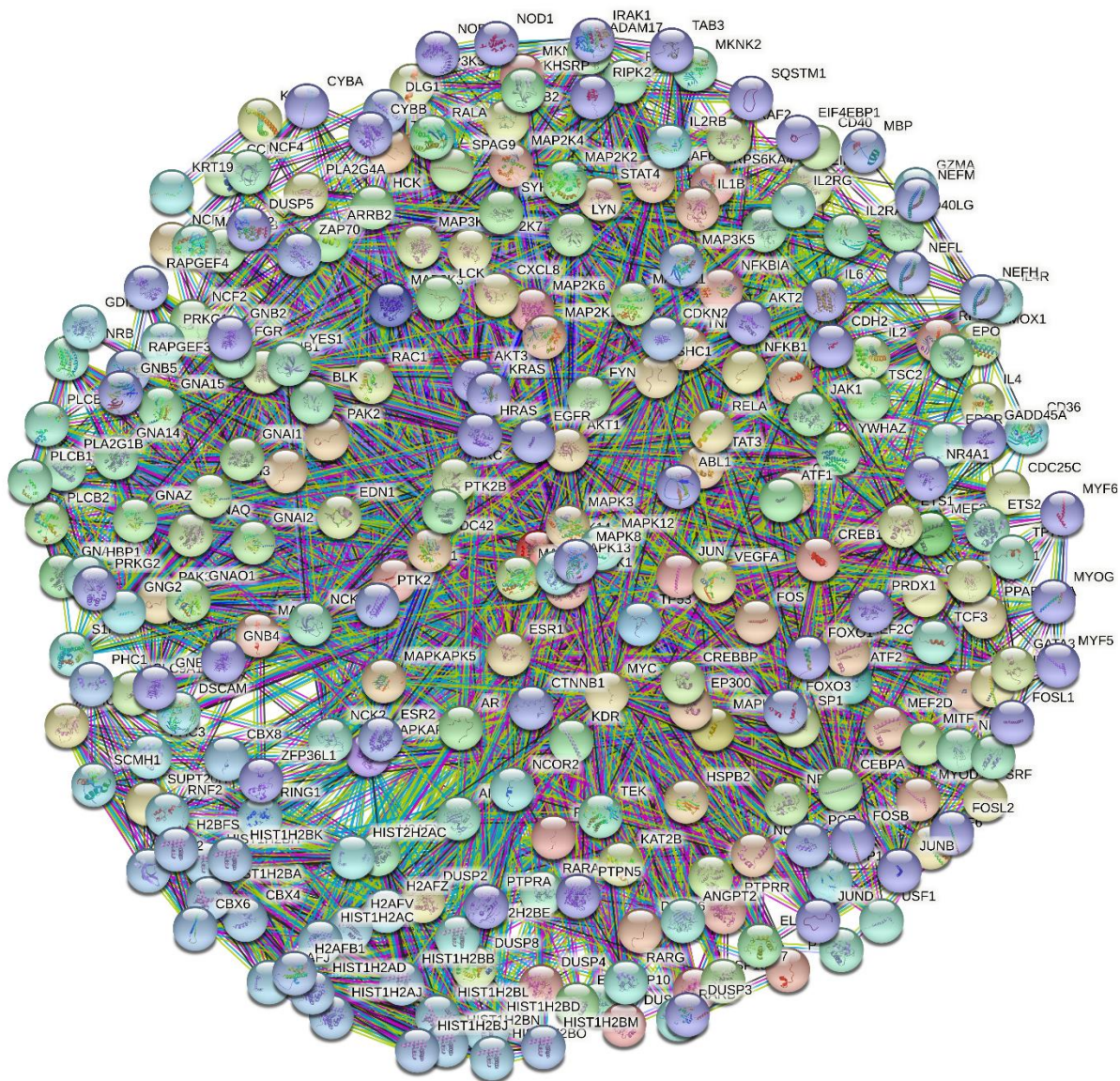


**Aggregation hot-spots**

**E**

There is no AlphaFold2 generated 3D structure for this protein at FuzDrop



**F**

minimum required interaction score: high confidence (0.700)

number of nodes: 263

number of edges: 3555

average node degree: 27

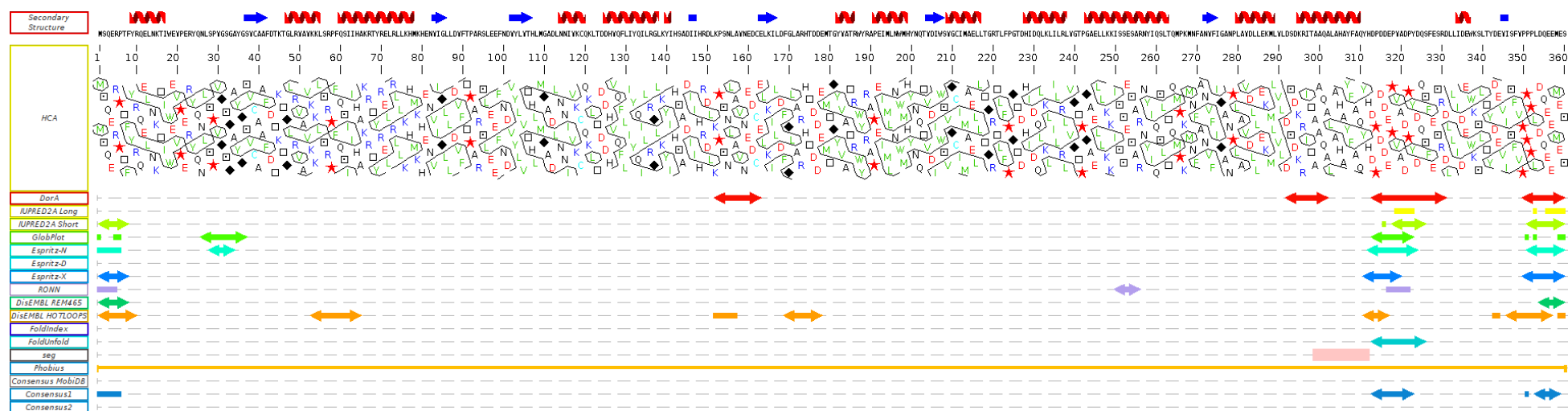
avg. local clustering coefficient: 0.621

expected number of edges: 1281

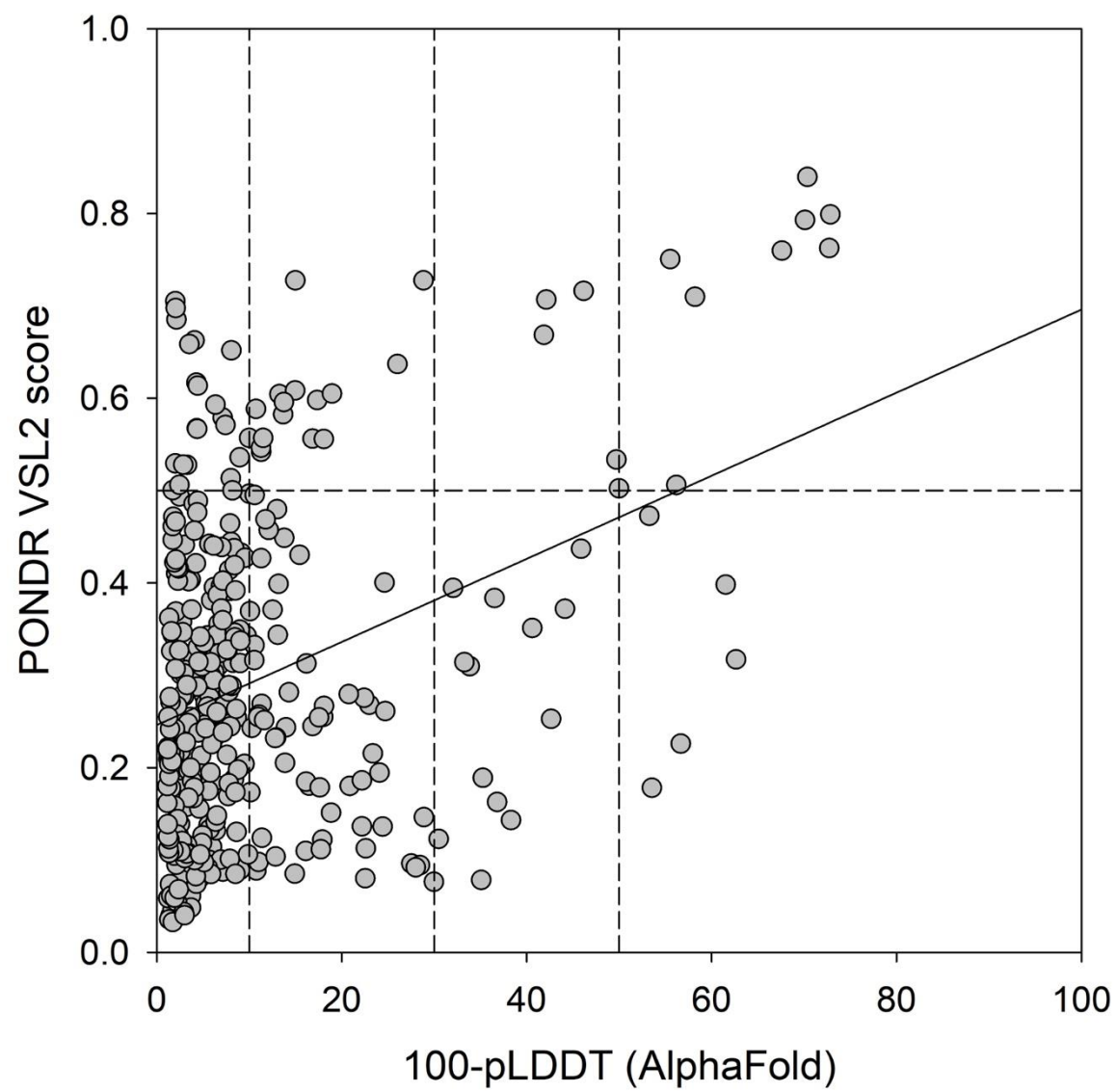
PPI enrichment p-value:  $< 1.0e-16$



G



H

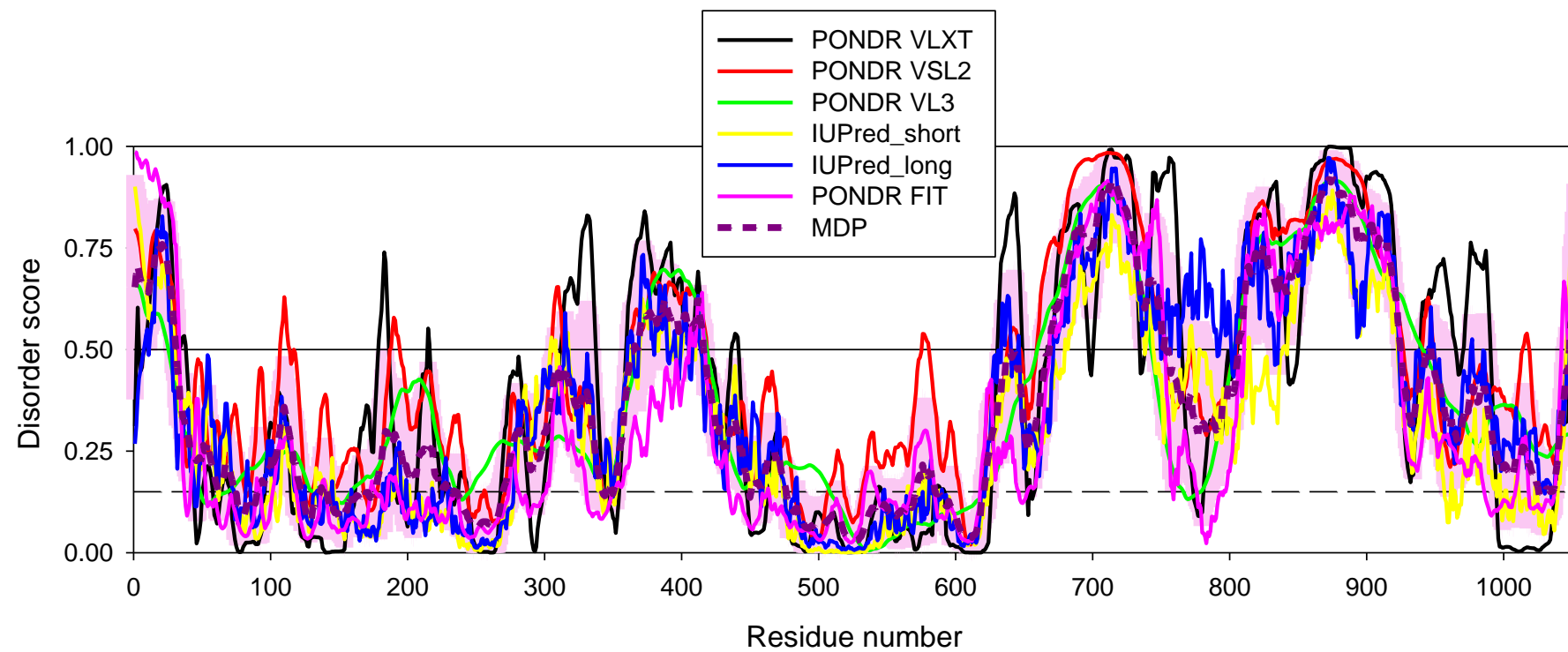


**Supplementary Figure S12.** Functional disorder in focal adhesion kinase 1. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the *per residue* disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

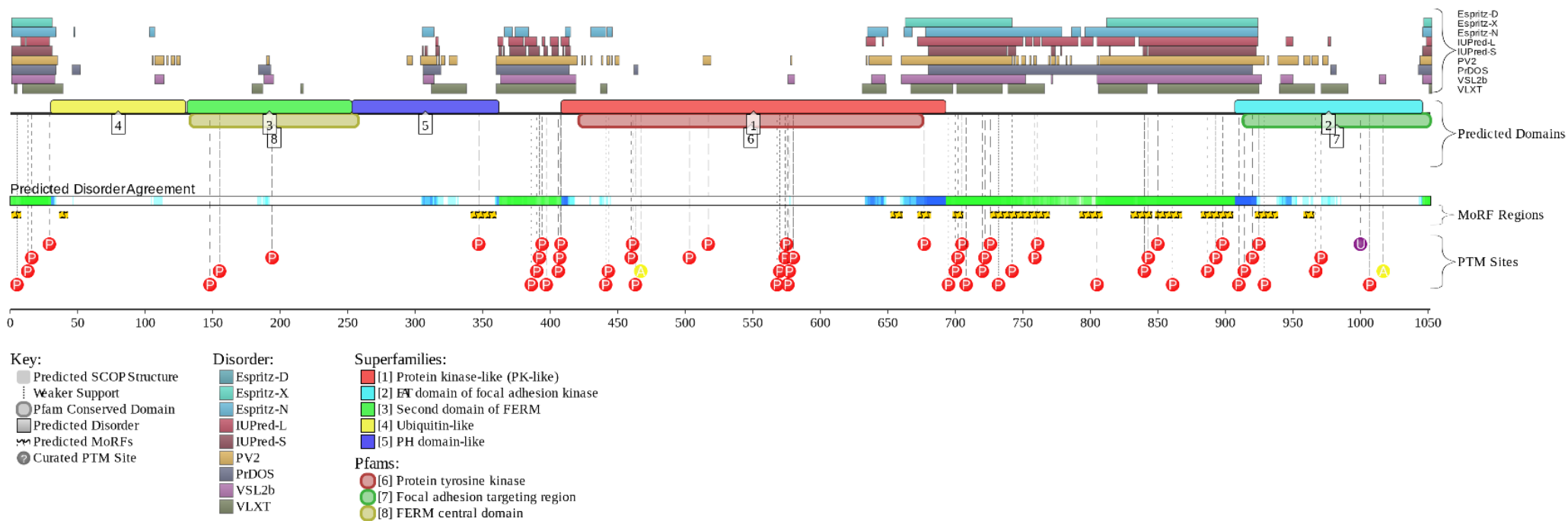
## A

>sp|Q05397|FAK1\_HUMAN Focal adhesion kinase 1 OS=Homo sapiens OX=9606 GN=PTK2 PE=1 SV=2

MAAAYLDPNLNHTPNSSSTKTHLGTGMERSPGAMERVLKVFHYFESNSEPTTWASIIRHGDATDVRGIIQKIVDSHKVVKHVACYGFRLSHLRSEEVHVLHVDMGVSSVREKYELAHPPE  
 EWKYELRIRYLPKGFLNQFTEDKPTLNFFYQQVKSDYMLEIADQVDQEIALKLGCLEIRRSYWEMRGNALAKKSNEYEVLEKDVGLKRFFPKSLLDSVKAKTLRKLIQQTFRQFANLNR  
 EESILKFFEILSPVYRFDKECFKCALGSSWIIISVELAIGPEEGISYLTDKGCNPTHLADFTQVQTIQYSNSEDKDRKGMLQLKIAGAPEPLTVTAPSLTIAENMADLIDGYCRLVNGT  
 SQSFIIRPQKEGERALPSIPKLANSEKQGMRTHAVSVSETDDYAEIIDEEDTYTMPSTRDYEIQRERIELGRCIGEGQFGDVHQGIYMSPENPALAVAIAKTCNKCTSDSVREKFLQEA  
 LTMRQFDHPPHIVKLIGVITENPVWIIIMELCTLGELRSFLQVRKYSLDLASLILYAYQLSTALAYLESKRFFVHRDIAARNVLVSSNDCVKLGDFGLSRYMEDSTYYKASKGKLPIKWMA  
 PESINFRRFTSASDVWMFGVCMWEILMHGVKPFQGVKNNDVIGRIENGERLPMPPNCPPTLYSLMTKCWAYDPSRRPRFTELKAQLSTILEEEKAQQEERMESRRQATVSWDSGGS  
 DEAPPKPSRPGYPSPRSSEGFYPSQHMVQTNHYQVSGYPGSHGITAMAGSIYPGQASLLDQTDSDWNHRPQEIAMWQPNVEDSTVLDLRGIGQVLPHTLMEERLIRQQQEMEEDQRWL  
 EKEERFLKPDVRLSRGSIDREDGSLQGPIGNQHIYQPVGKPDPAAPPKKPPRPGAPGHLGSLASLSSPADSYNEGVKLQEQEISPPPTANLDRSNDKVYENVVTGLVKAVIEMSSKIQP  
 APPEEYVPMVKEVGLALRTLATVDETIPLLPASTHREIEMAQKLLNSDLGELINKMKLAQQYVMTSLQEQEYKKQMLTAAHALAVDAKNLLDVIDQARLKMLGQTRPH

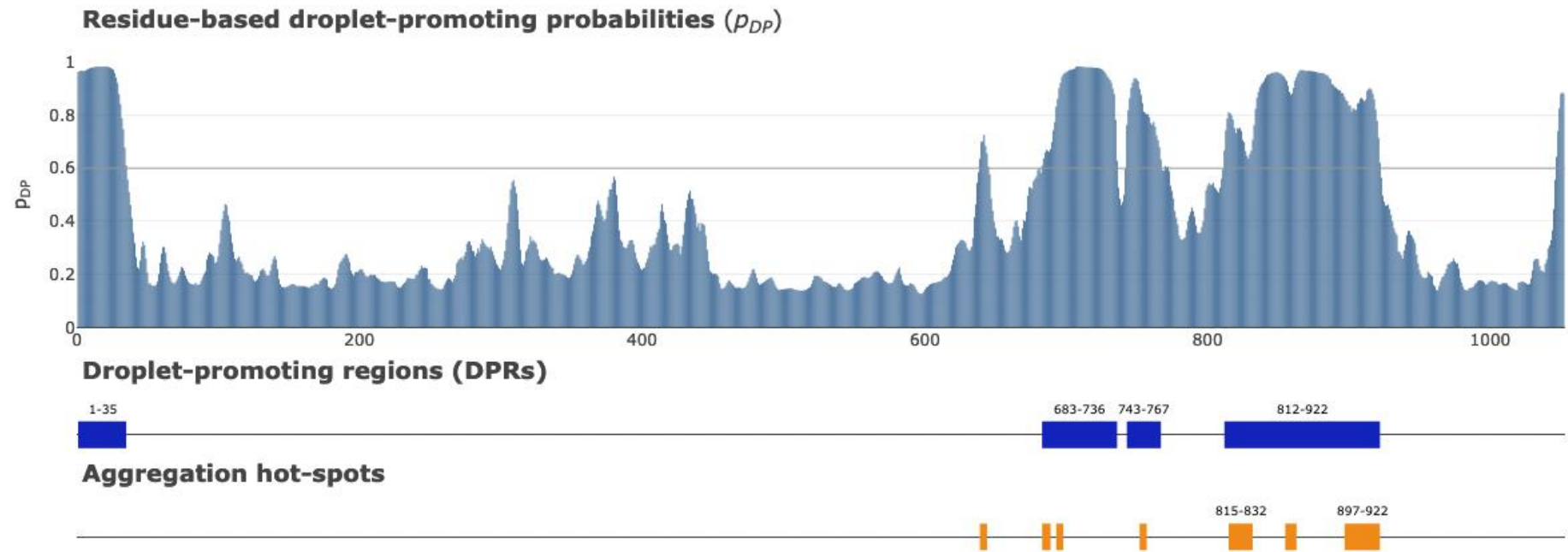
**B**

C

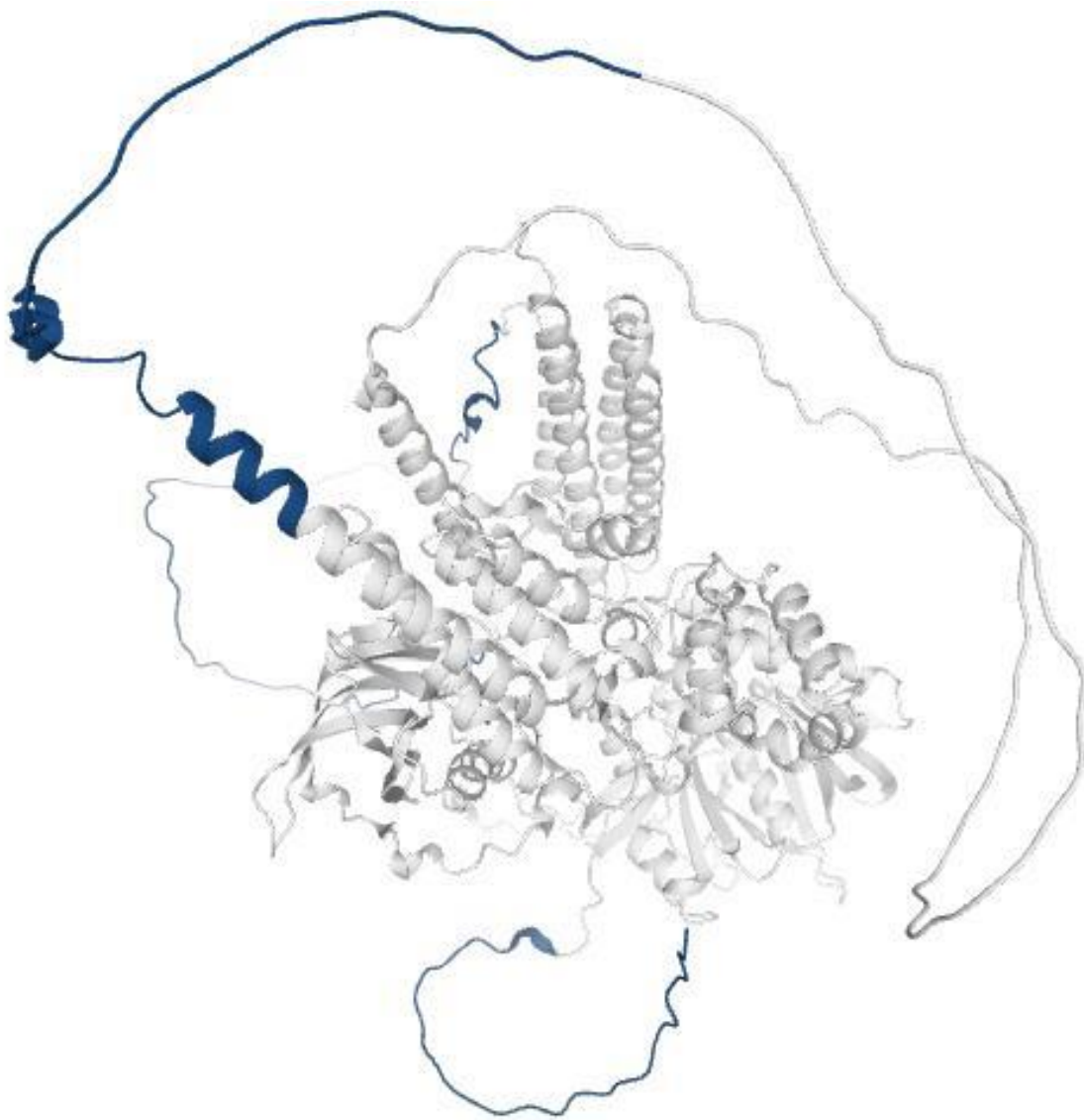


D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.6417$

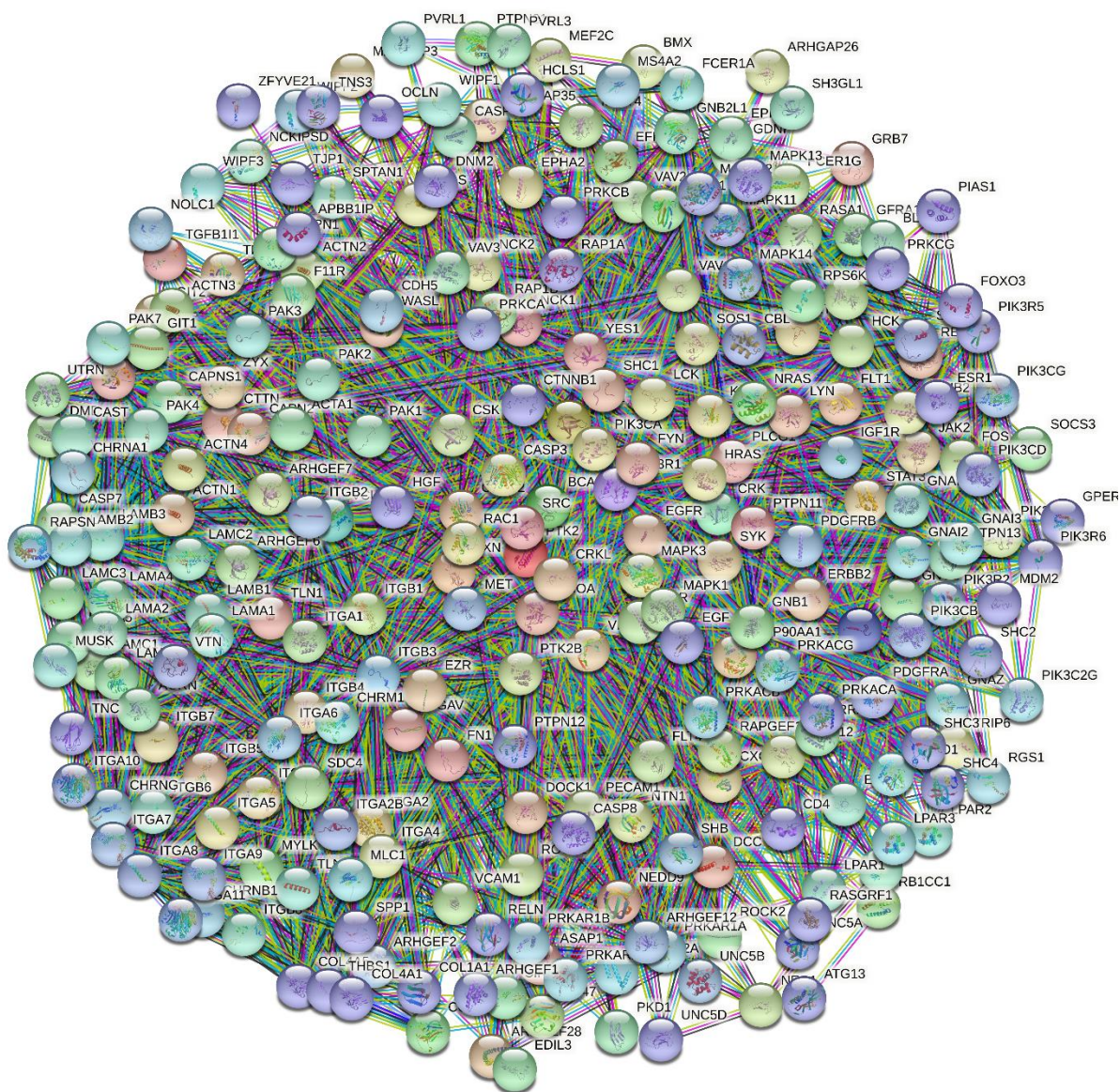


E





**F**



minimum required interaction score: high confidence (0.700)

number of nodes: 263

number of edges: 5082

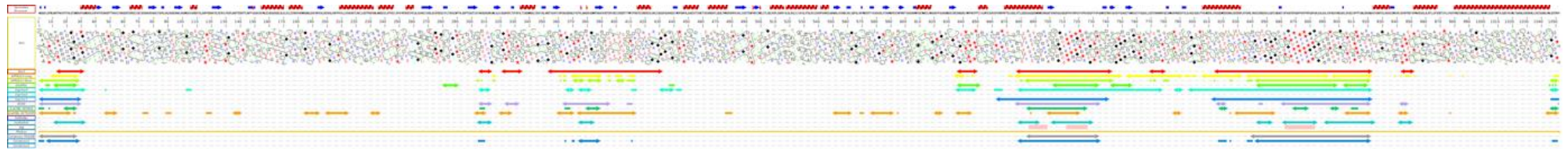
average node degree: 38.6

avg. local clustering coefficient: 0.605

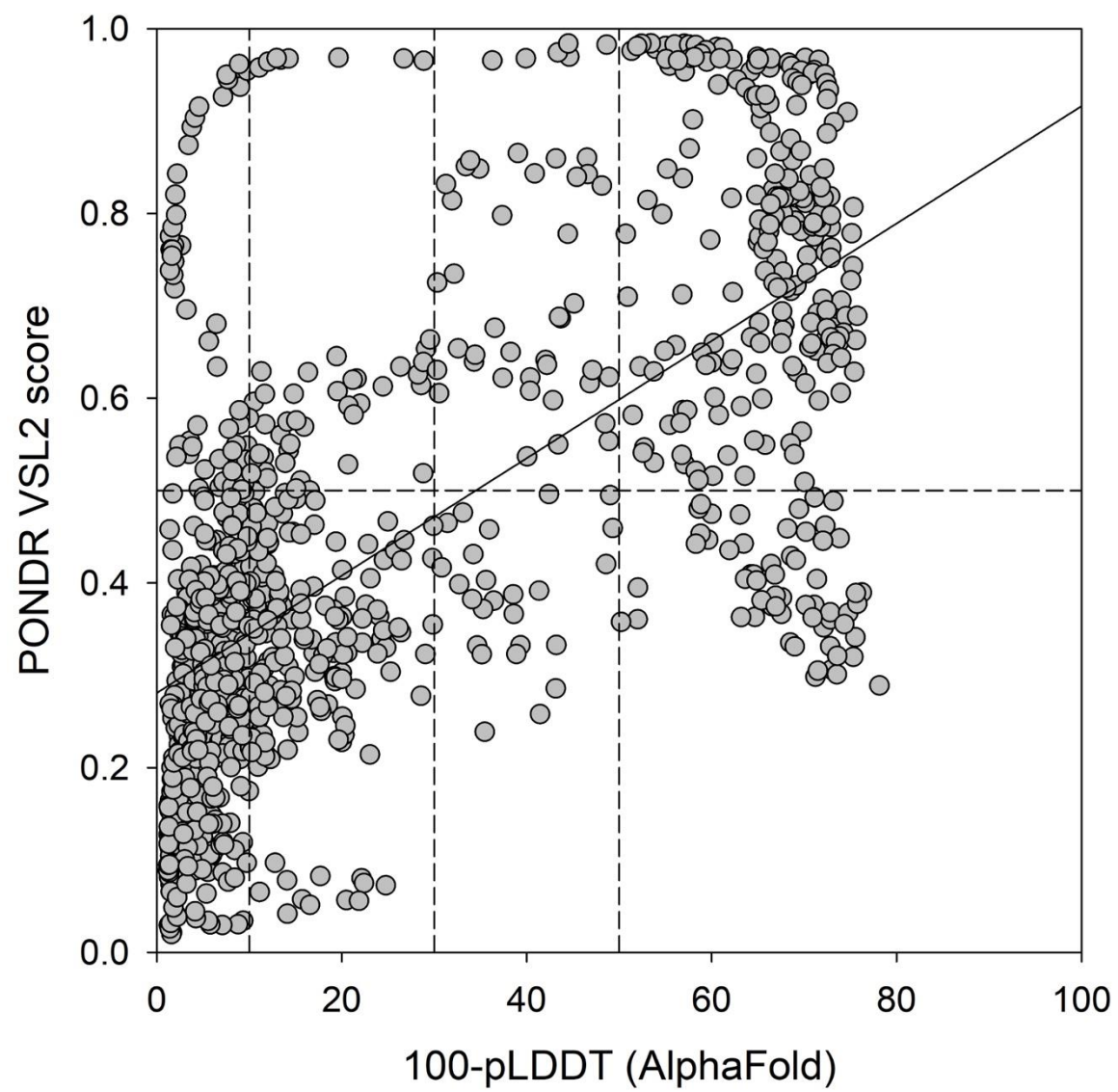
expected number of edges: 1183

PPI enrichment p-value:  $< 1.0e-16$

G



H

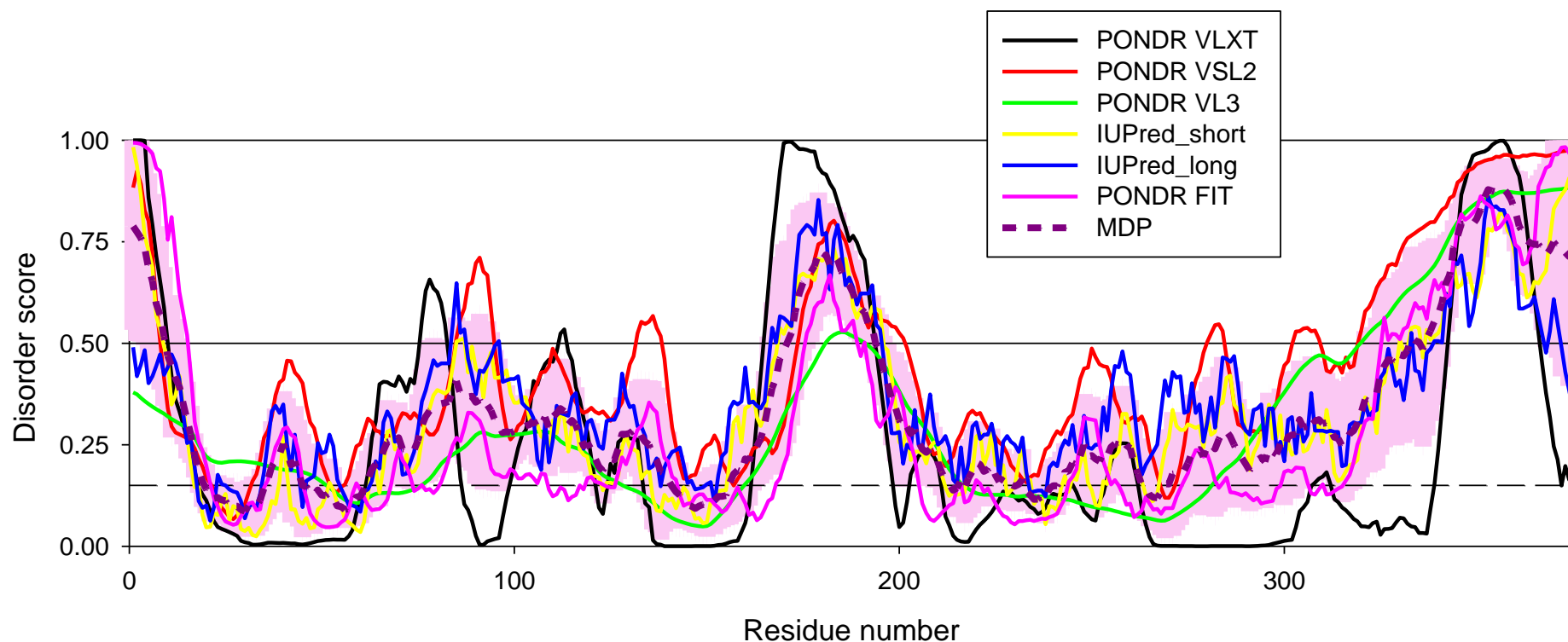


**Supplementary Figure S13.** Functional disorder in nucleolysin TIAR. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

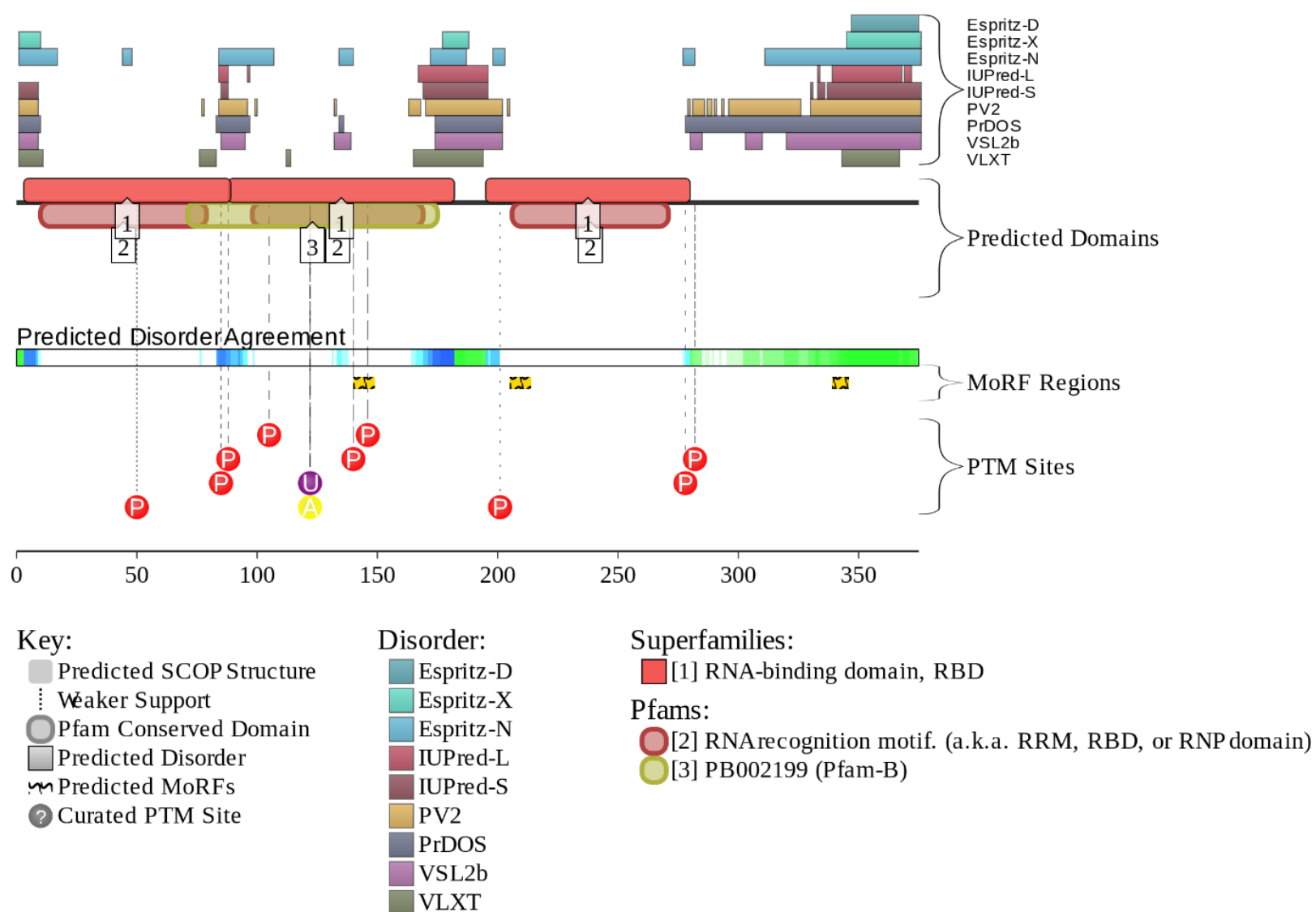
```
>sp|Q01085|TIAR_HUMAN Nucleolysin TIAR OS=Homo sapiens OX=9606 GN=TIAL1 PE=1 SV=1
MMEDDGQPRTLVGNLSRDVTEVLILQLFSQIGPCKSCKMITEHTSNDPYCFVEFYEHRDAAAALAAMNGRKILGKEVKVNWATTPSSQKKDTSNHFHVFGDLSP EITTEDIKSAFA
PFGKISDARVVKDMATGKSKGYGFVSFYNKLDAENAIIVHMGQWLGGRIQRTNWATRKPAPKSTQENNTKQLRFEDVVNQSSPKNCTVYCGGIASGLTDQLMRQTFSPFGQIMEIRV
FPEKGSFVRFTSTHSAHAIVSVNGTTIEGHVVKCYWGKESPDMTKNFQQVDYSQWGQWSQVYGNPQQYGQYMANGWQVPPYGVYGPWNQQGFGVDQSPSAAWMGGFQAQPPQGQA
PPPVIPPNQAGYGMASYQTQ
```

**B**



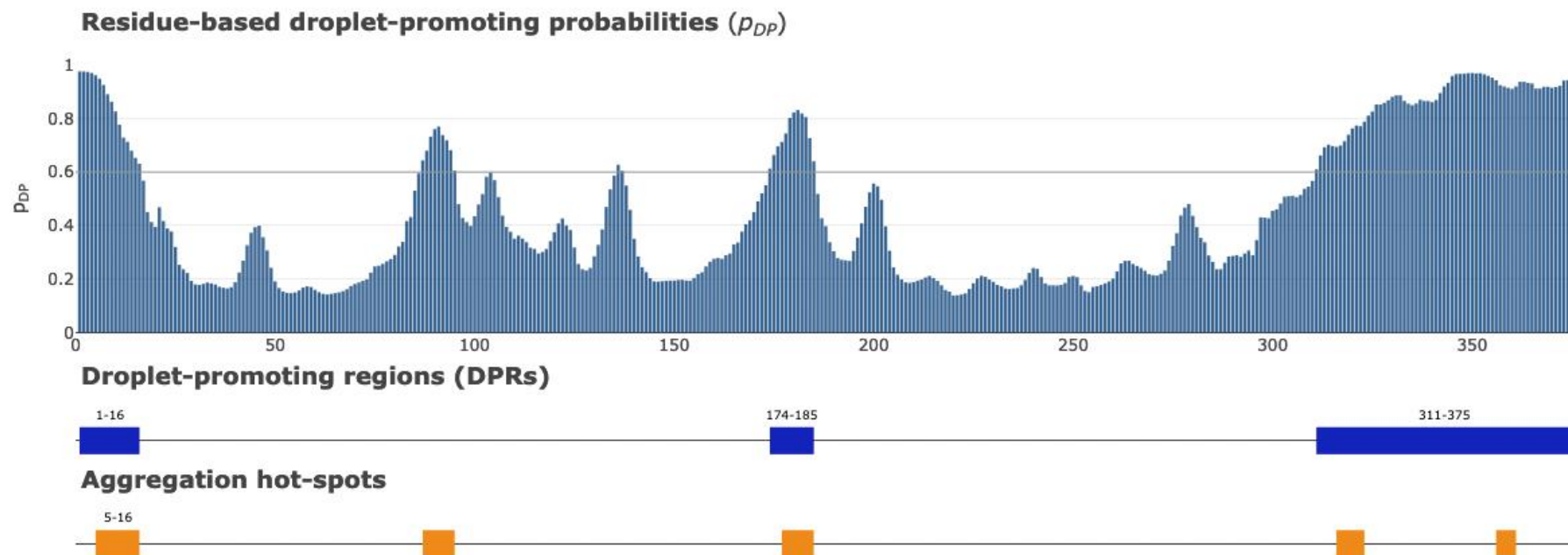


C

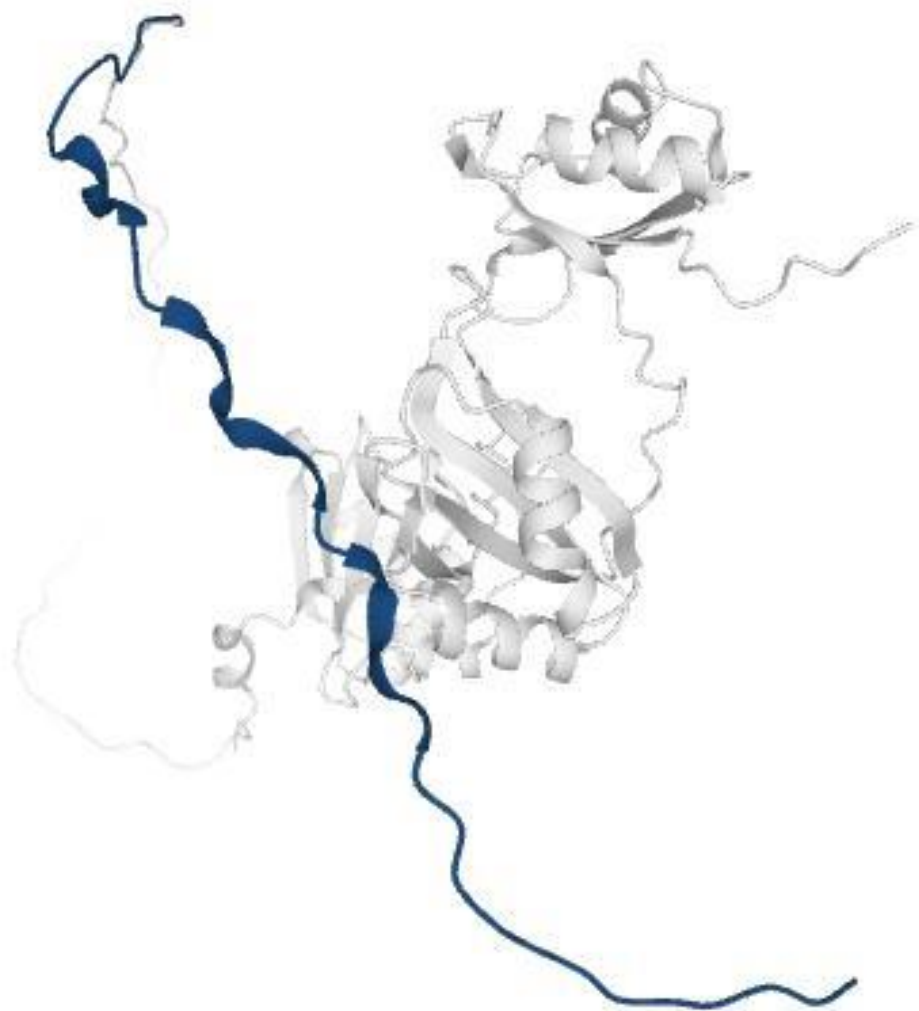


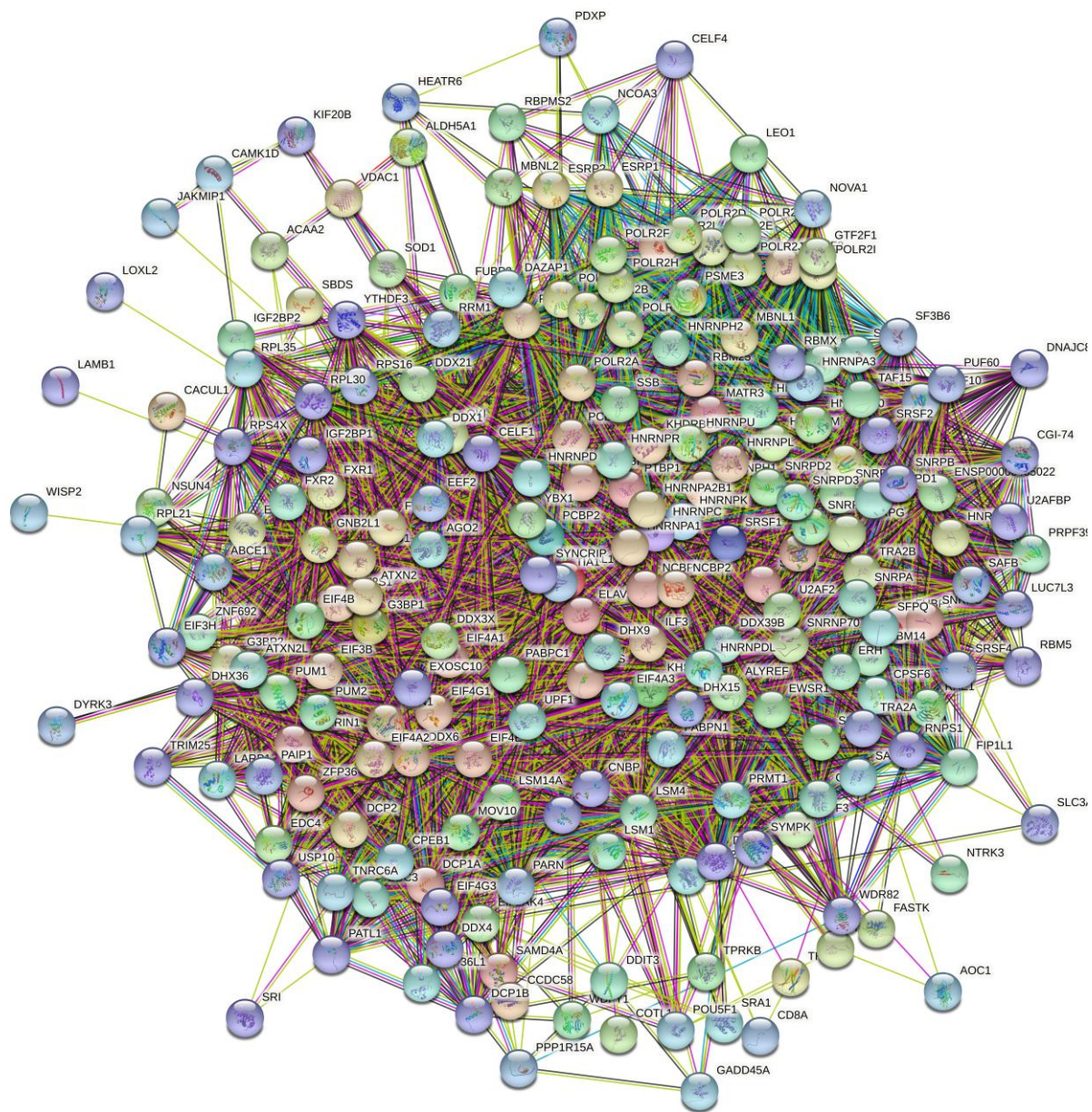
D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.5758$









**F**

minimum required interaction score: medium confidence (0.400)

number of nodes: 222

number of edges: 6457

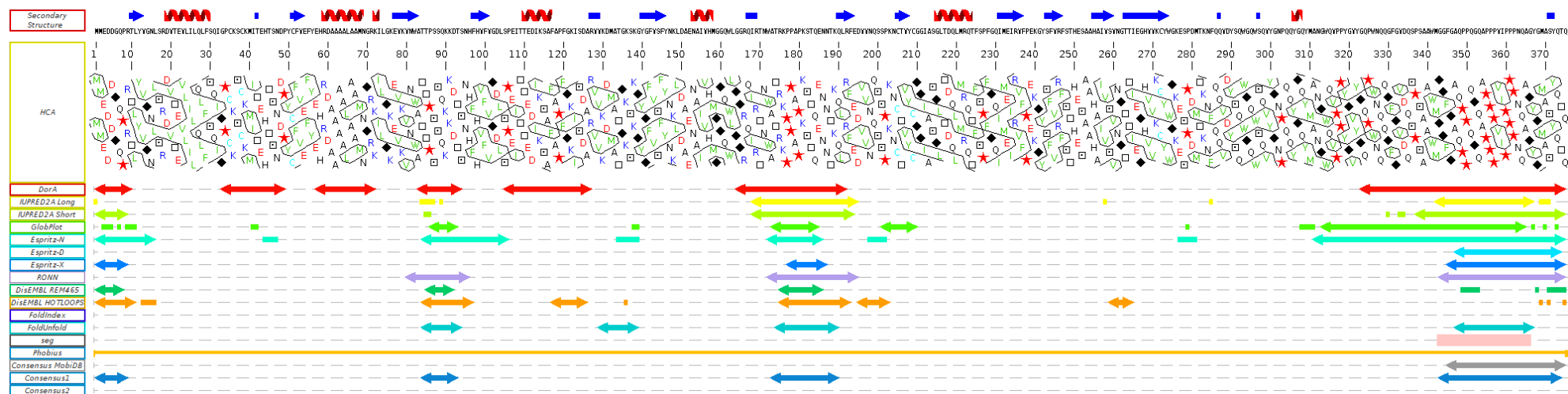
average node degree: 58.2

avg. local clustering coefficient: 0.669

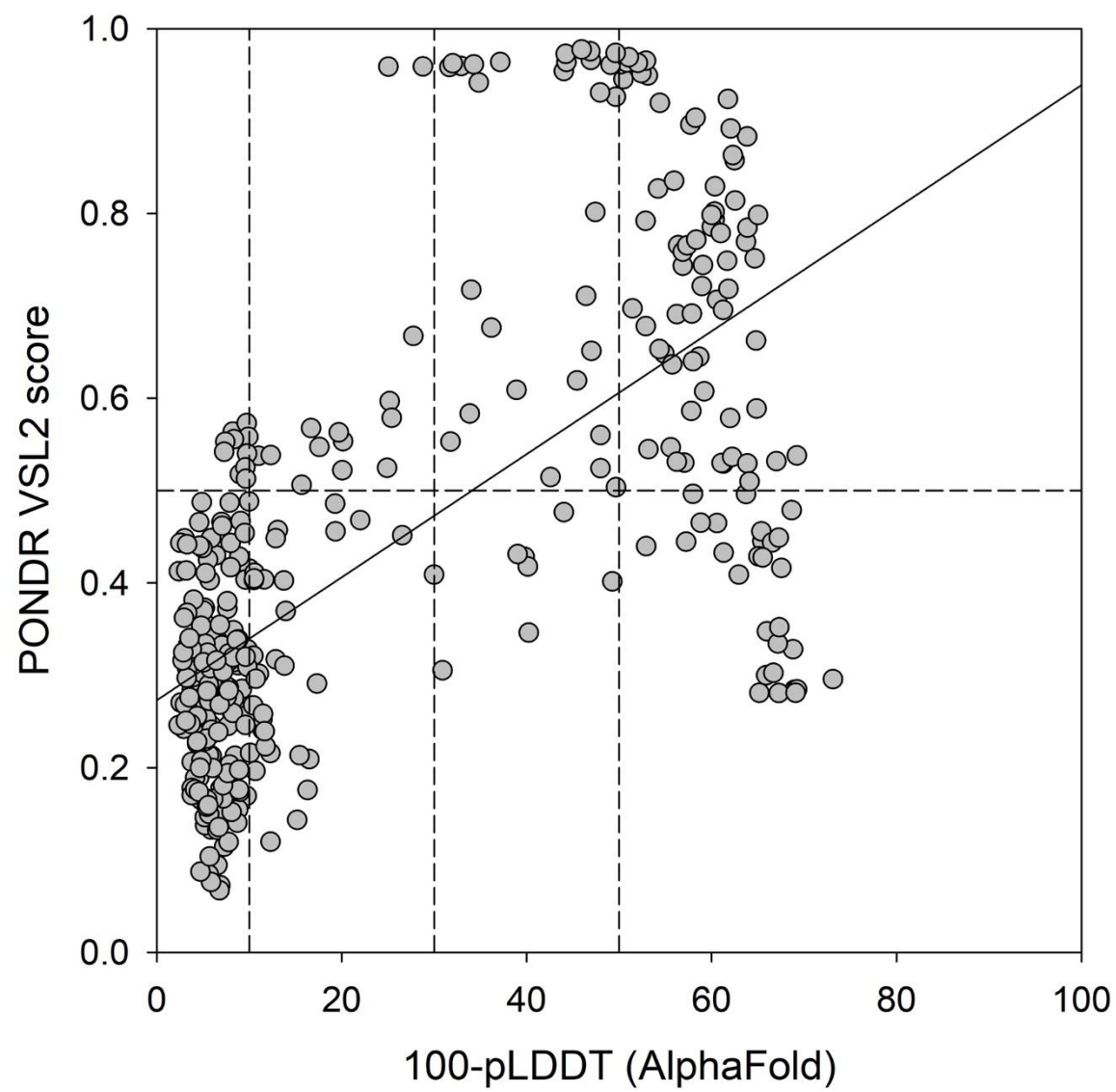
expected number of edges: 1131

PPI enrichment p-value:  $< 1.0e-16$

G



H

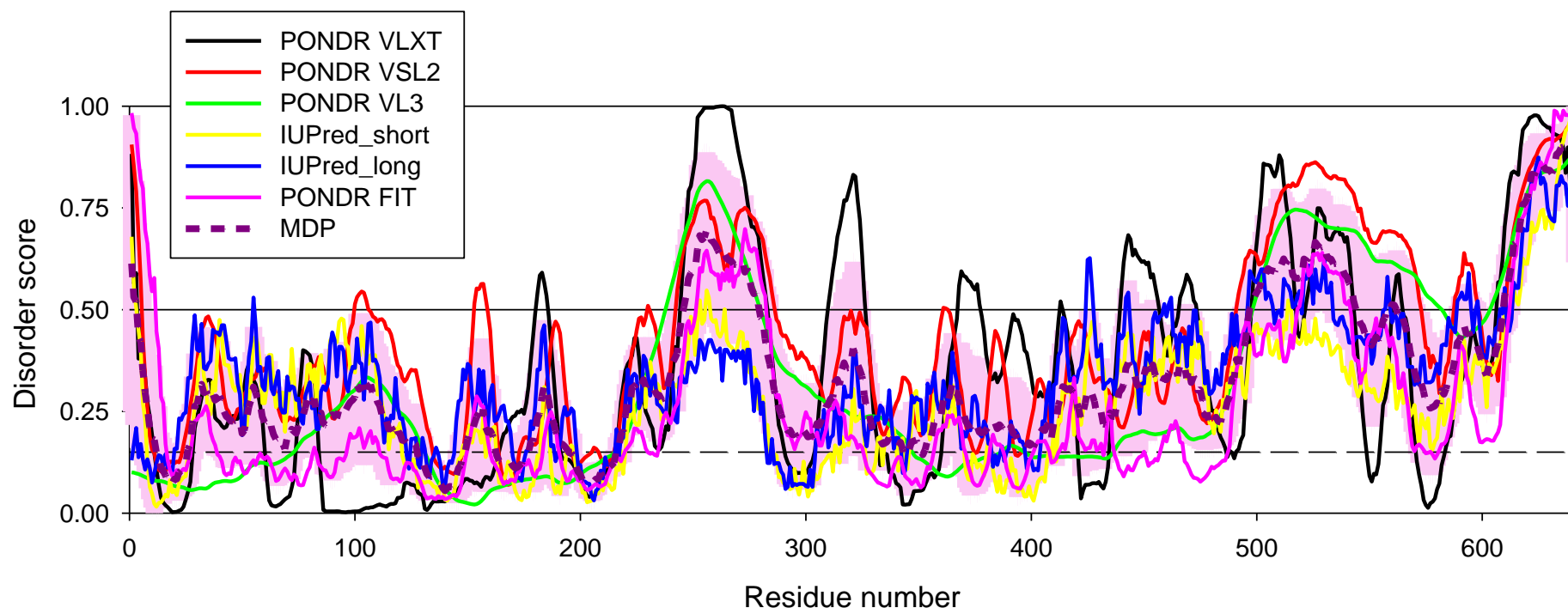


**Supplementary Figure S14.** Functional disorder in heat shock 70 kDa protein 1A. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

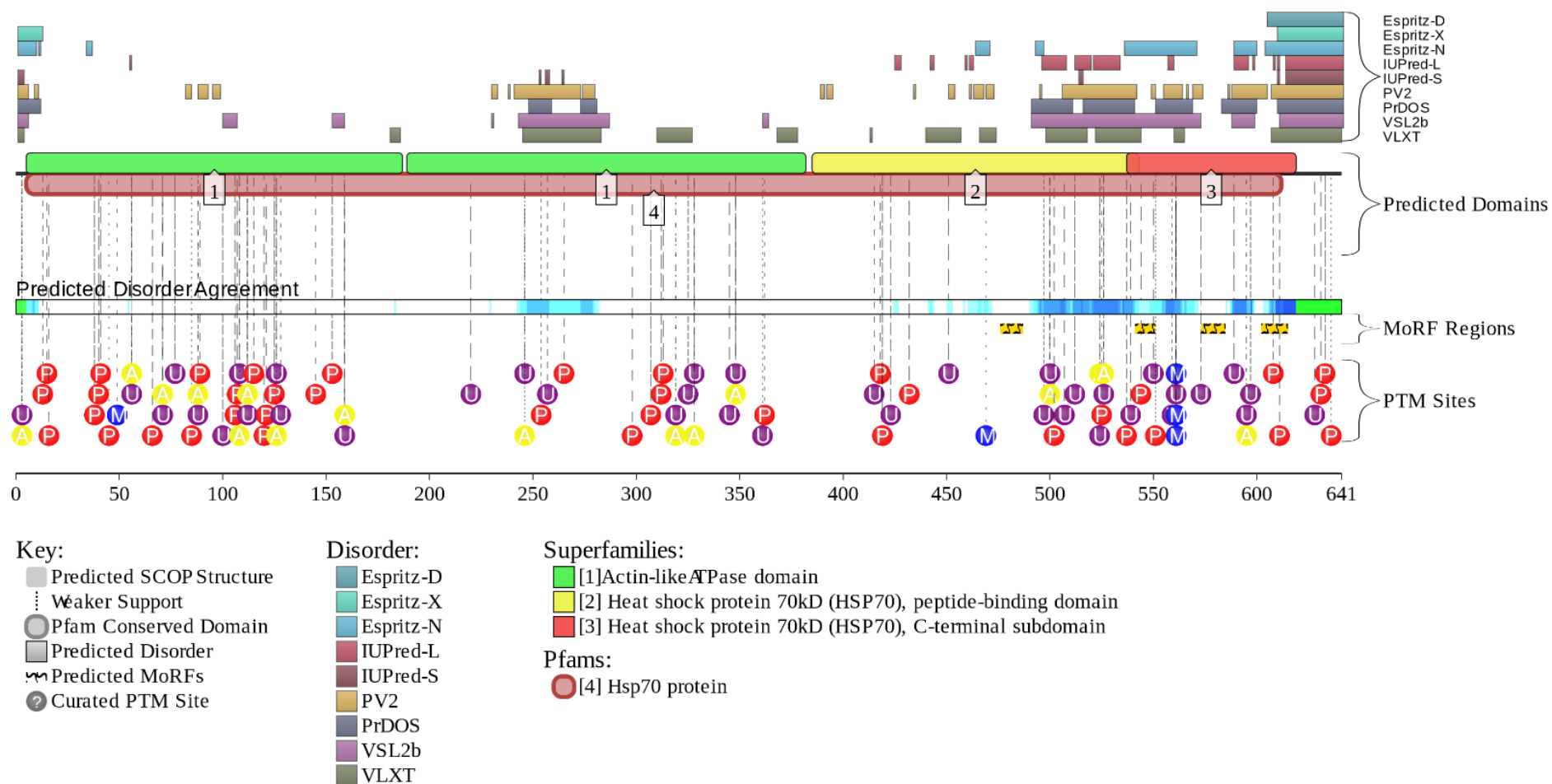
```
>sp|P0DMV8|HS71A_HUMAN Heat shock 70 kDa protein 1A OS=Homo sapiens OX=9606 GN=HSPA1A PE=1 SV=1
MAKAAAIGIDLGTYSVGVFQHGKVEIIANDQGNRTTPSYVAFTDTERLIGDAAKNQVALNPQNTVFDKRLIGRKFGDPVVQSDMKHWPFQVINDGDKPKVQVSYKGETKAFYPEE
ISSMVLTKMKEIAEAYLGYPVTNAVITVPAYFNDSQRQATKDAGVIAGLNVLRINEPTAAAIAYGLDRTGKGERNVLIFDLGGGTFDVSILTIDDGIFEVKATAGDTHLGGEDFDNR
LVNHFVEEFKRKHKKDISQNKRAVRLRTACERAKRTLSSSTQASLEIDSLFEGIDFYTSITRARFEELCSDLFRSTLEPVEKALRDAKLDKAQIHDVLVLVGGSTRI PKVQKLLQDFF
NGRDLNKSINPDEAVAYGA AVQAAILMGDKSENVQDLLLLDVAPLSLGLTAGGVM TALIKRNSTIPTKQTQIFTTYS DNQPGVLIQVYEGERAMTKDNNLLGRFELSGIPPAPRGVP
QIEVTFDIDANGILNVTATDKSTGKANKITITNDKGRLSKEEIERMVQEA EKYKA EDEVQRERVS AKNALESYAFNMKSAVEDEGLKGKISEADKKKVLDKQCQEVISWLDANTLAEKD
EFEHKRKELEQVCNPIISGLYQGAGGPGPGGFGA QGPKGGSGSGPTIEEVD
```

**B**





C

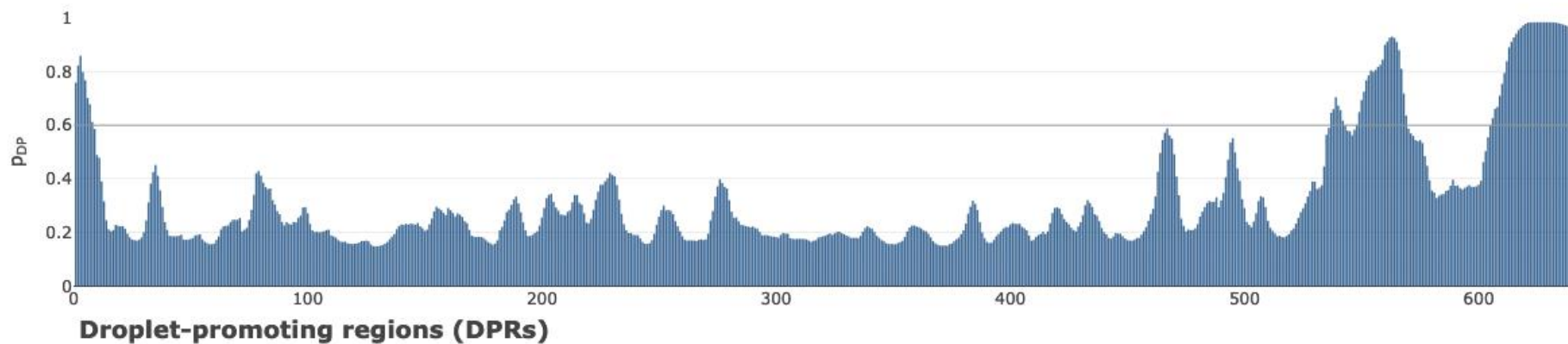




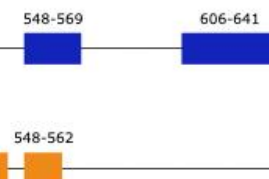
D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.3928$

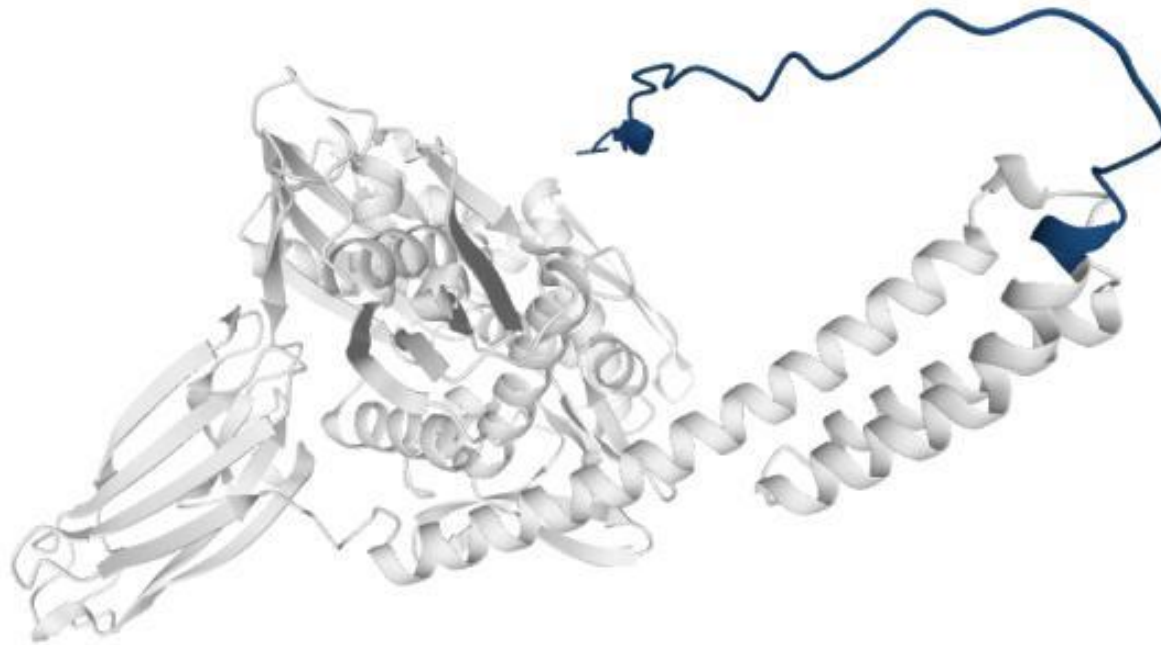
**Residue-based droplet-promoting probabilities ( $p_{DP}$ )**

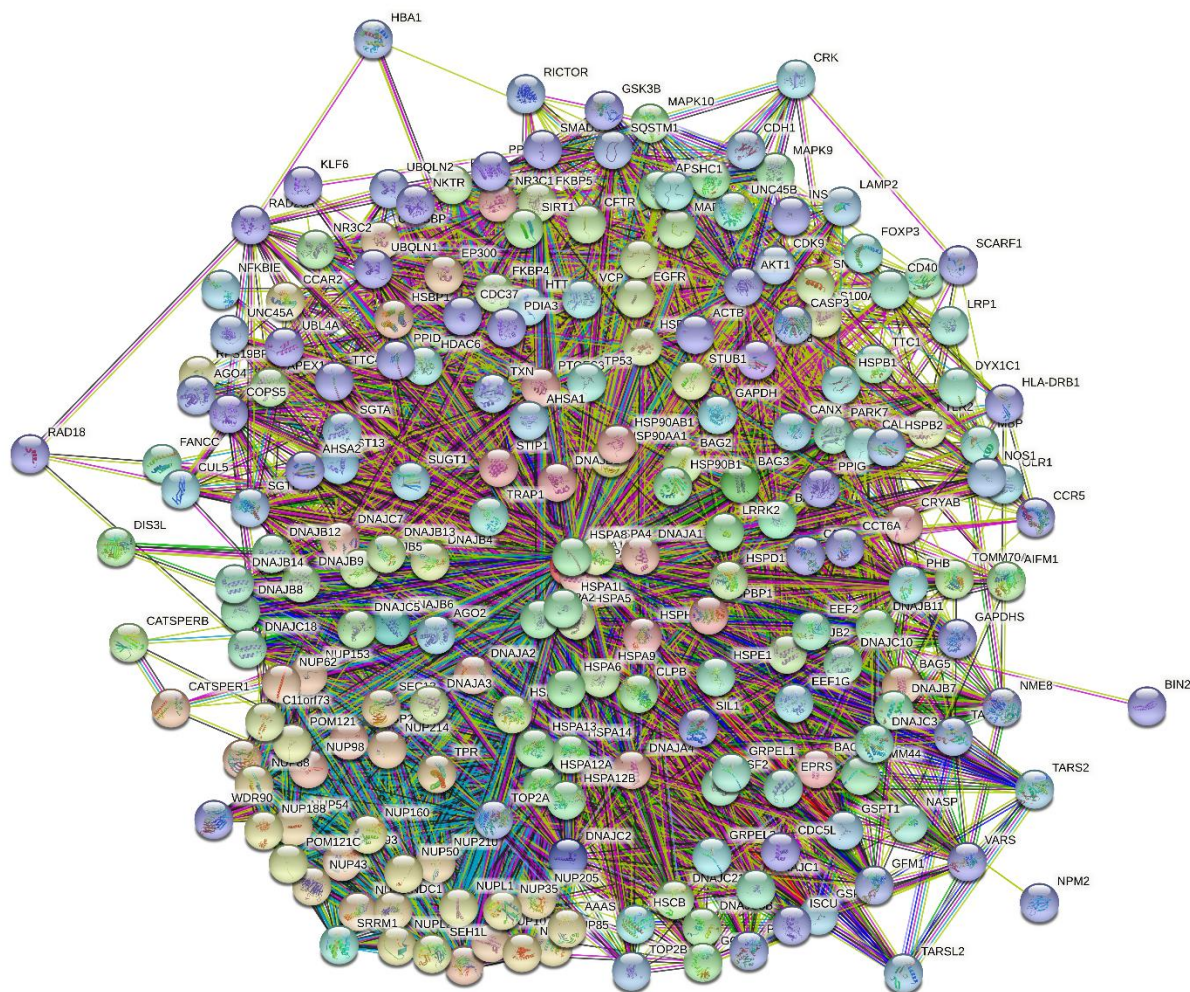


**Aggregation hot-spots**



**E**



**F**

minimum required interaction score: medium confidence (0.400)

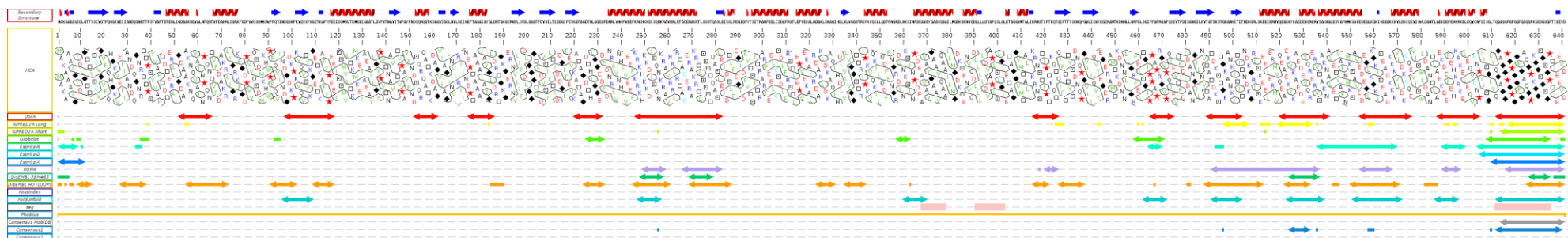
number of nodes: 215

number of edges: 4876

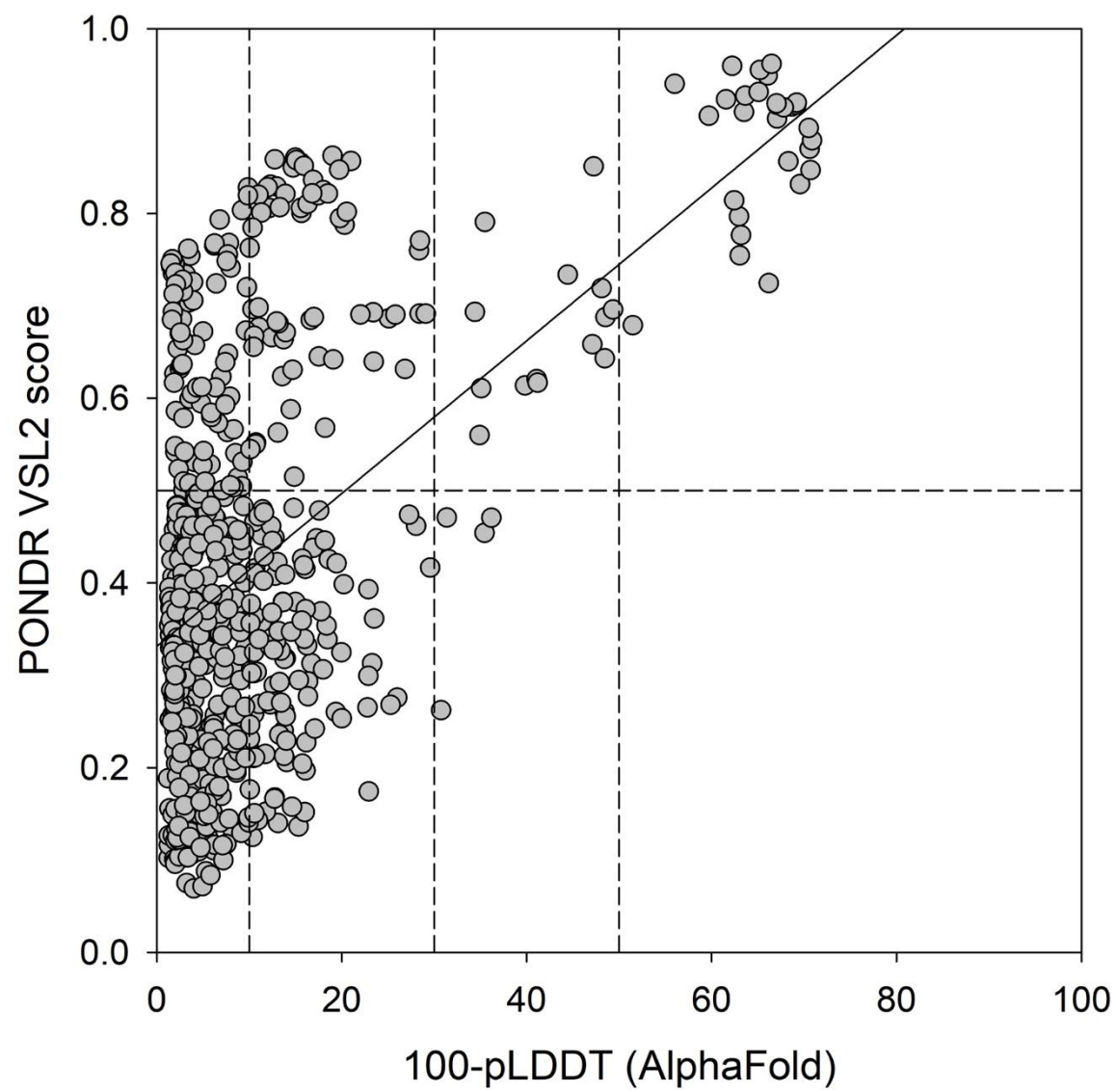
average node degree: 45.4

avg. local clustering coefficient: 0.697  
expected number of edges: 1281  
PPI enrichment p-value:  $< 1.0e-16$

**G**



H

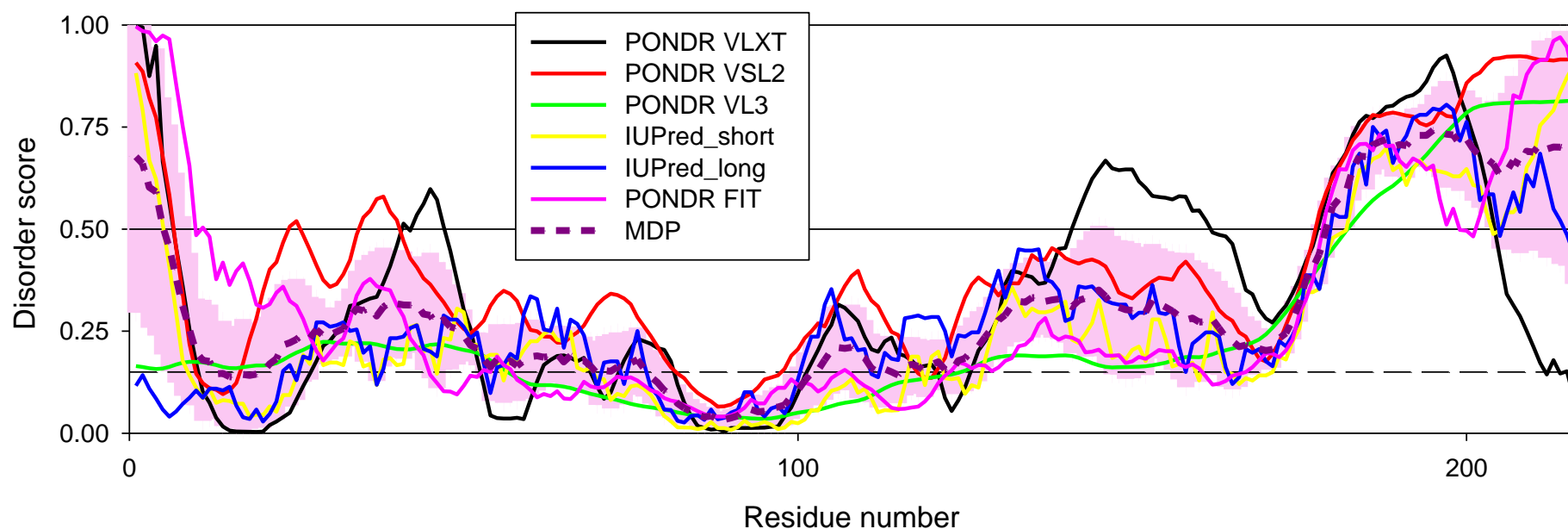


**Supplementary Figure S15.** Functional disorder in Ras-related protein Rab-11A. **A.** Amino acid sequence. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

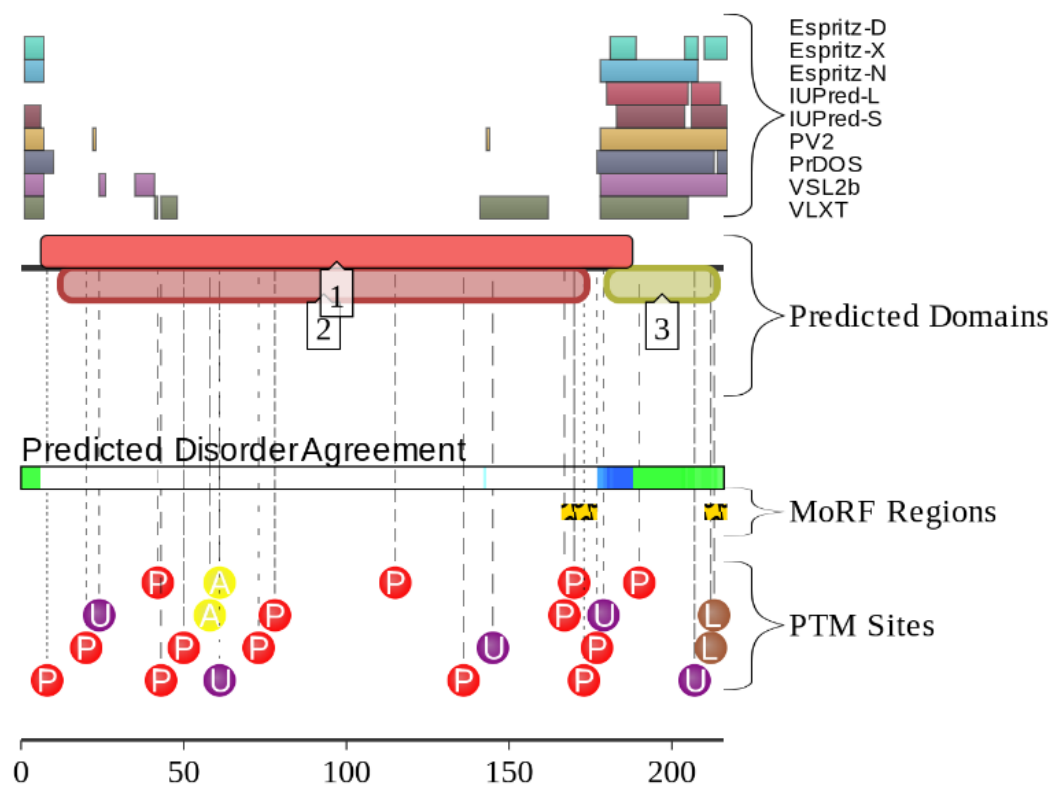
```
>sp|P62491|RB11A_HUMAN Ras-related protein Rab-11A OS=Homo sapiens OX=9606 GN=RAB11A PE=1 SV=3
MGTRDDEYDYLFKVVLLIGDSGVGKSNLLSRFTRNEFNLESKSTIGVEFATRSIQVDGKTIKAQIWDTAGQERYRAITSAYYRGAVGALLVYDIAKHLTYENVERWLKELRDHADSNI
IMLVGNKSDLRHLRAVPTDEARAFKNGLSFIETSA LDSTNVEAAFQTILTEIYRIVSQKQMSDRRENDMSPSNNVVPPIHVPPTTENKPKVQCCQNI
```

**B**





C



Key:

- Predicted SCOP Structure
- ⋮ Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- ⋈ Predicted MoRFs
- Curated PTM Site

Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

Superfamilies:

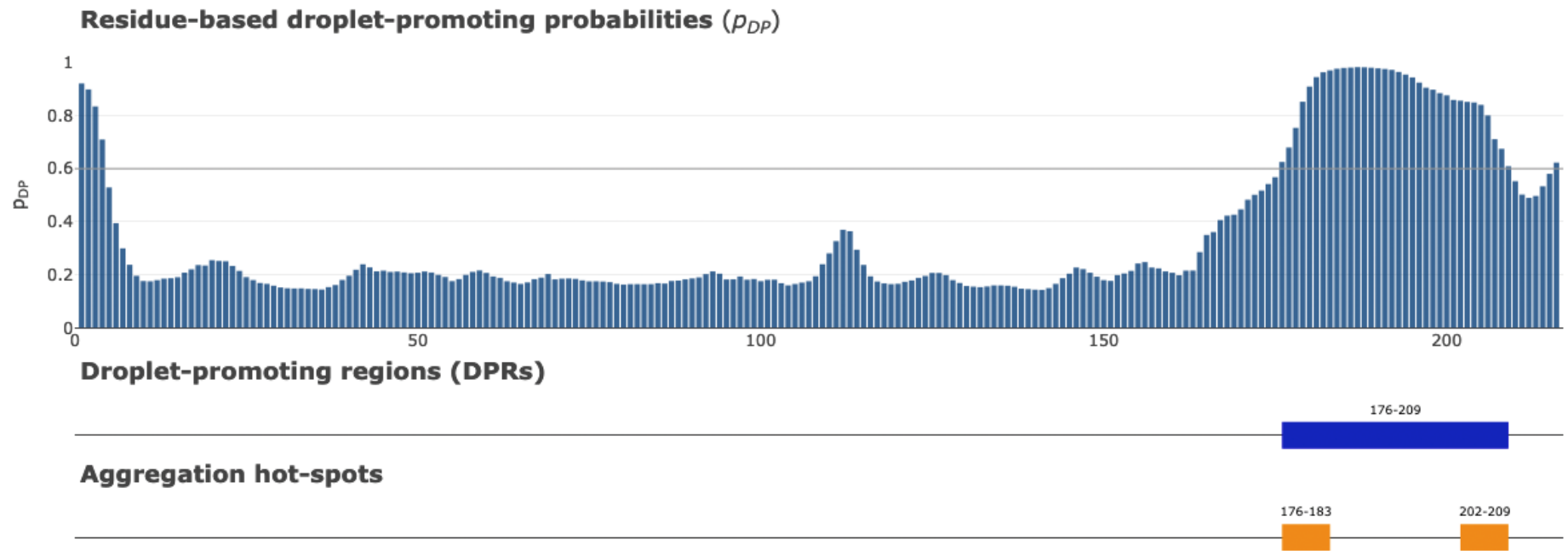
- [1] P-loop containing nucleoside triphosphate hydrolases

Pfams:

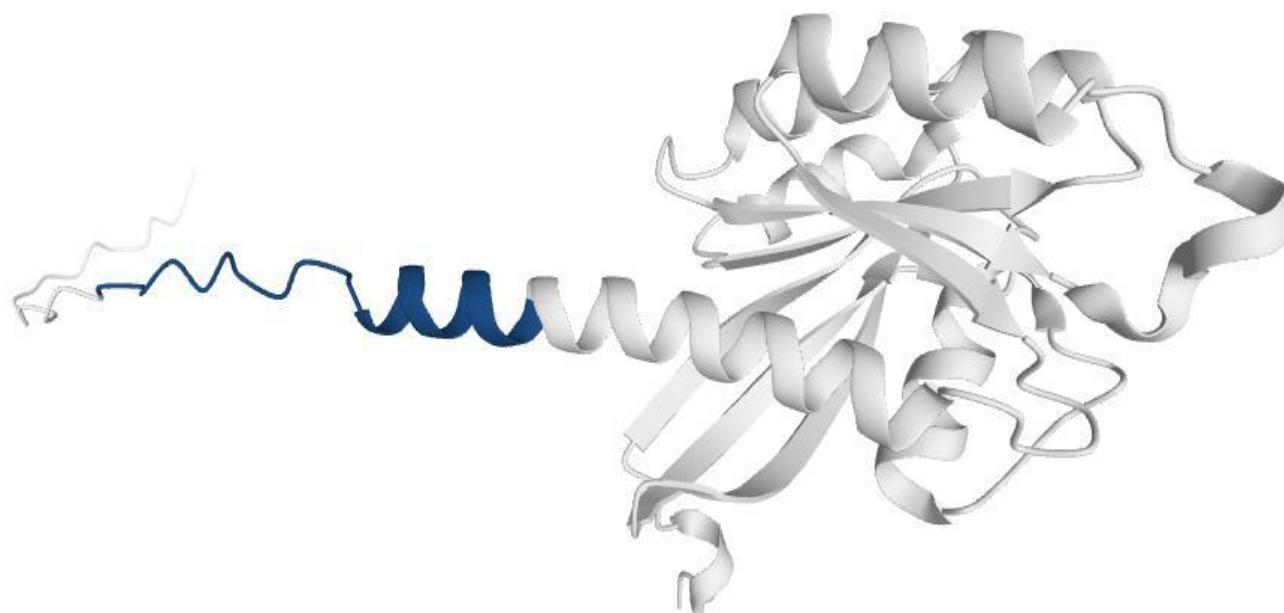
- [2] Ras family
- [3] PB012238 (Pfam-B)

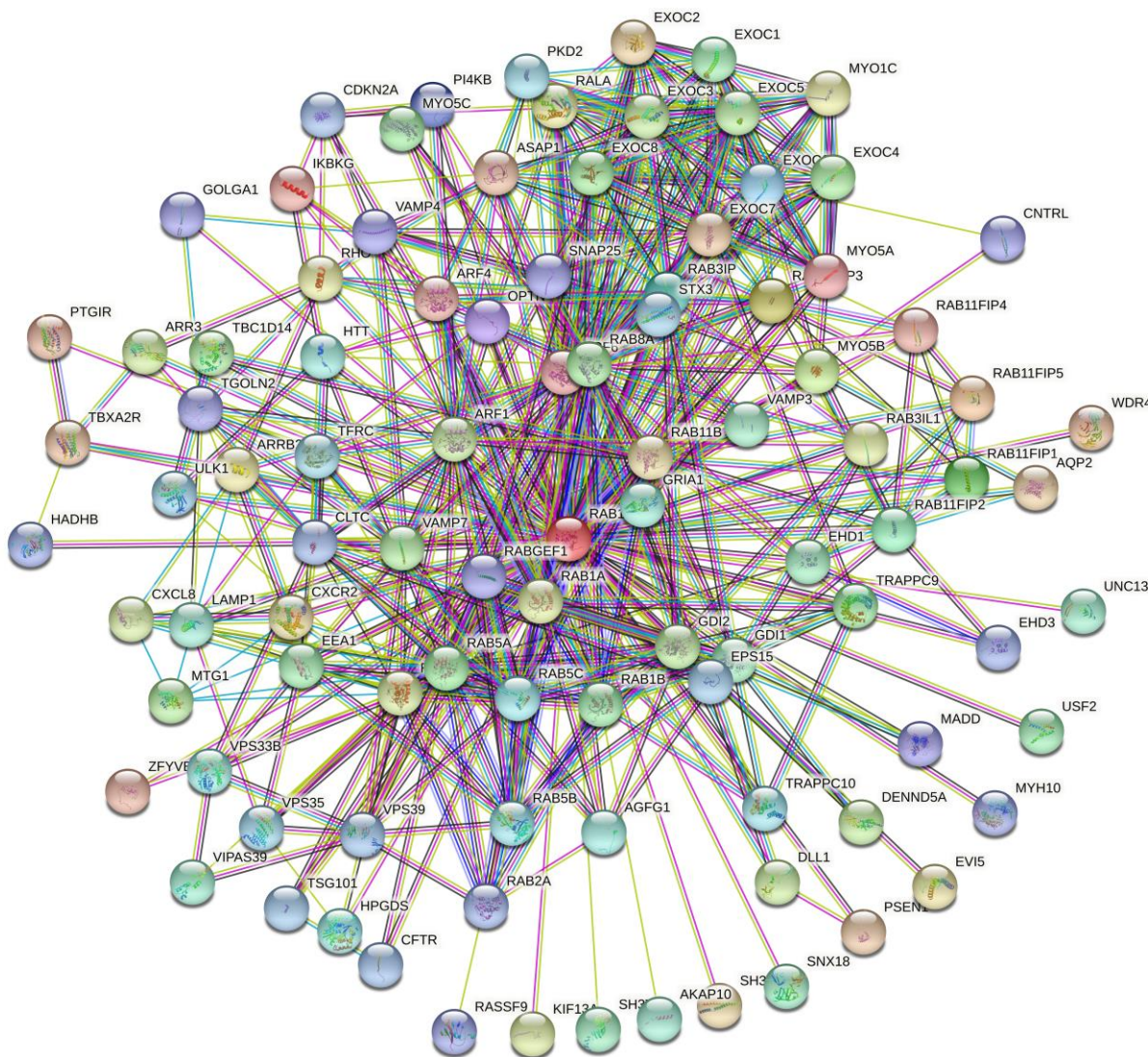
D

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.1679$



**E**

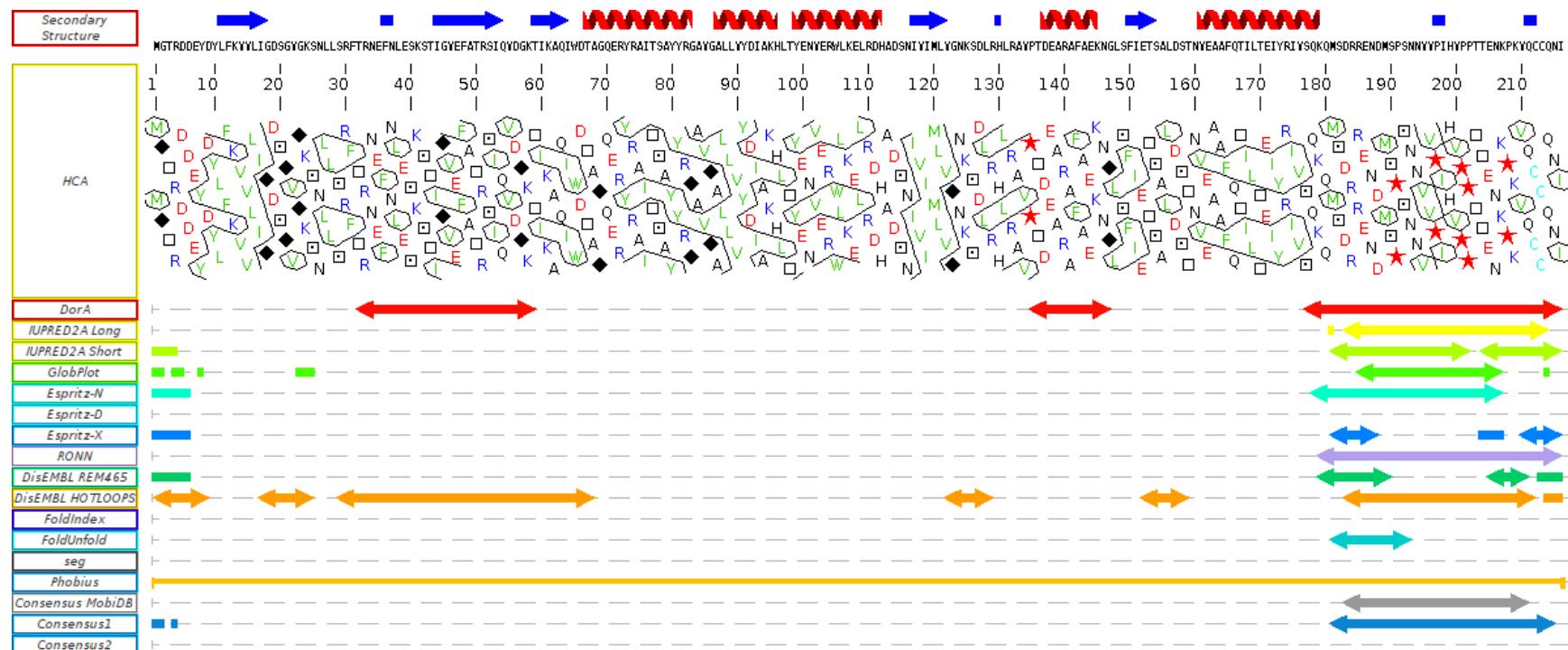


**F**

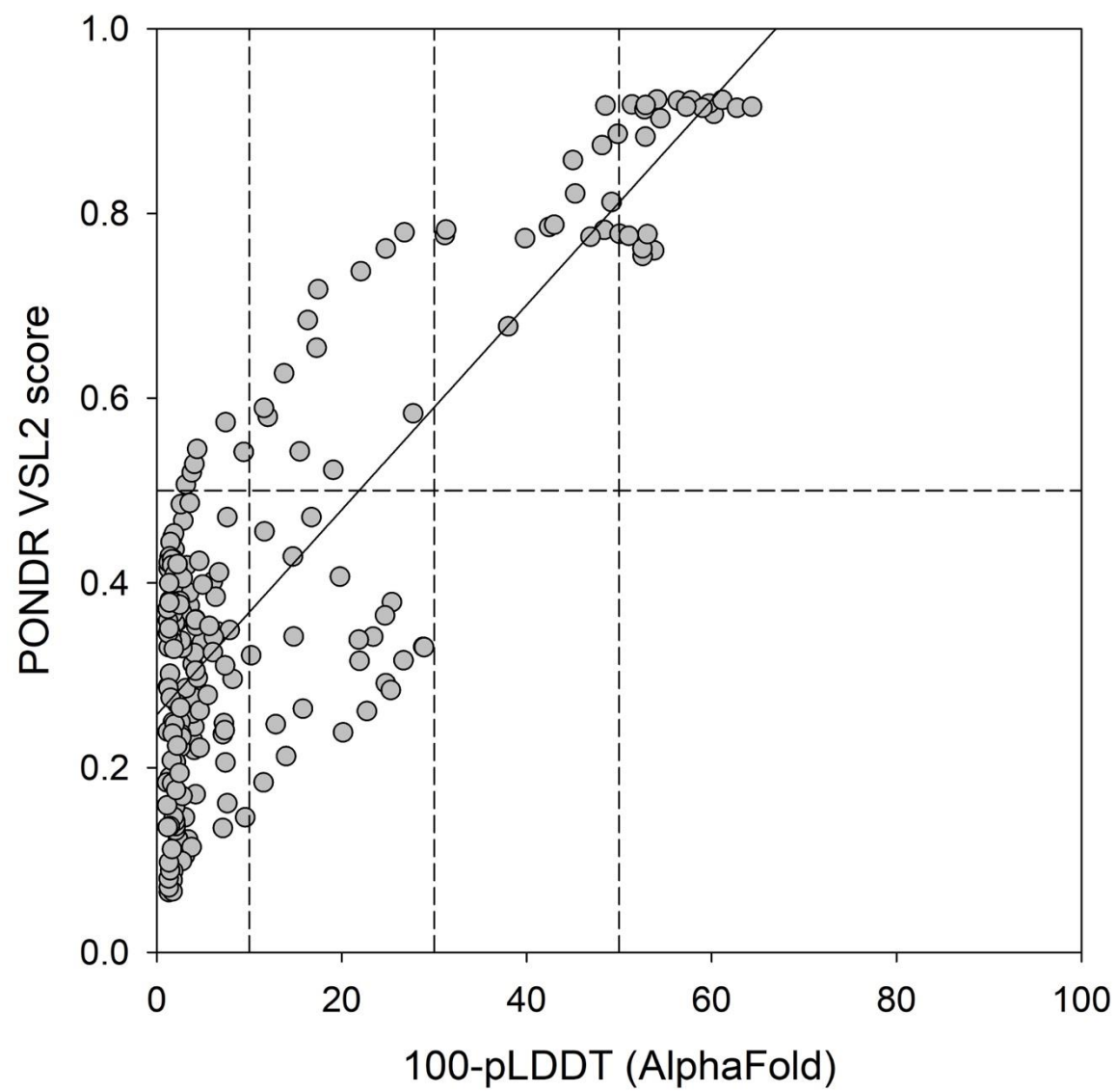
minimum required interaction score: high confidence (0.700)

number of nodes: 97  
number of edges: 485  
average node degree: 10  
avg. local clustering coefficient: 0.699  
expected number of edges: 125  
PPI enrichment p-value:  $< 1.0e-16$

G



H



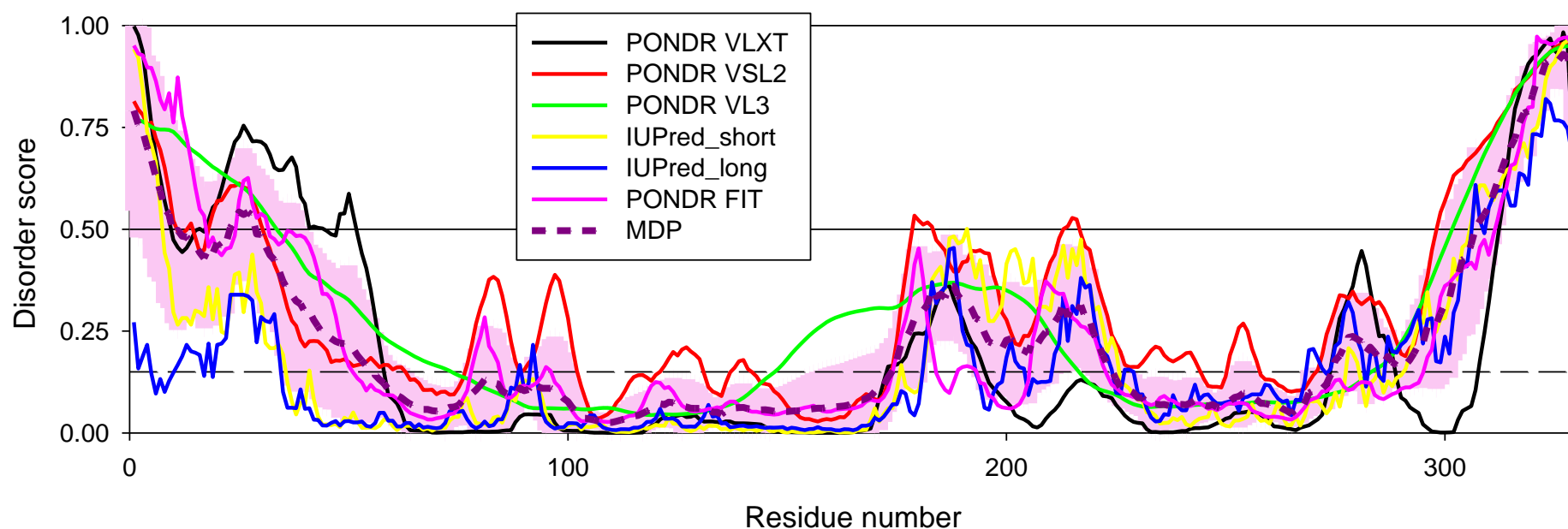


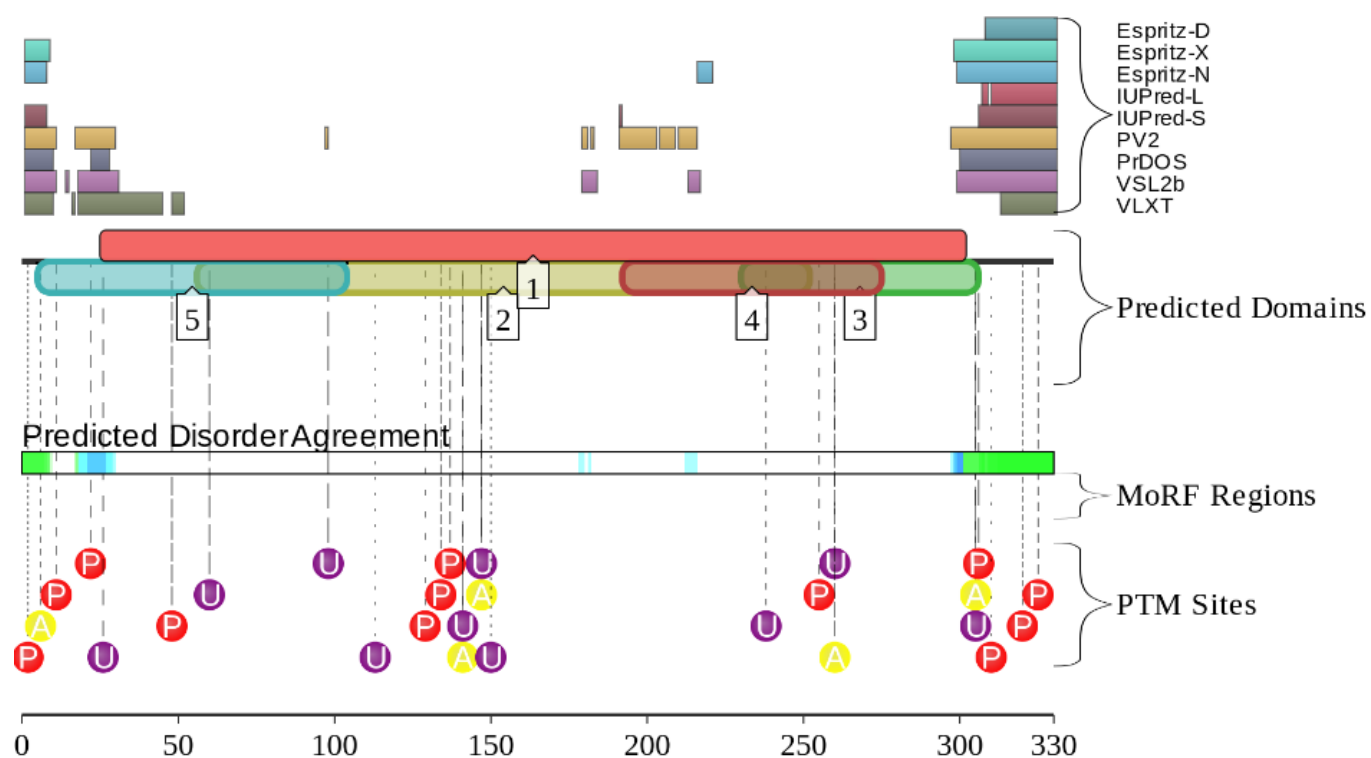
**Supplementary Figure S16.** Functional disorder in serine/threonine-protein phosphatase PP1-alpha catalytic subunit. **A.** Amino acid sequence. **B.** RDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>sp|P62136|PP1A_HUMAN Serine/threonine-protein phosphatase PP1-alpha catalytic subunit OS=Homo sapiens OX=9606
GN=PPP1CA PE=1 SV=1
MSDSEKLNLDSSIIGRLLEVQGSRPGKNVQLTENEIRGLCLKSREIFLSQPILLELEAPLKICGDIHGQYYDLLRLFYGGFPPESNYLFLGDYVDRGKQSLETICLLLAYKIKYPENF
FLLRGNHECASINRIYGFYDECKRRYNIKLWKTFTDCFNCLPIAAIVDEKIFCCHGGLSPDLQSMEQIRRIMRPTDVPDQGLLCDLLWSDPKDVKVQGWGENDRGVSFTTFGAENVAKFL
HKHDLDLICRAHQVVEDGYEFFAKRQLVTLFSAPNYCGEFDNAGAMMSVDETLMCSFQILKPADKNKGKYGFSGLNPGGRPITPPRNSAKAKK
```

**B**





### Key:

- Predicted SCOP Structure
- ⋮ Weaker Support
- Pfam Conserved Domain
- Predicted Disorder
- ~ Predicted MoRFs
- ⊙ Curated PTM Site

### Disorder:

- Espritz-D
- Espritz-X
- Espritz-N
- IUPred-L
- IUPred-S
- PV2
- PrDOS
- VSL2b
- VLXT

### Superfamilies:

- [1] Metallo-dependent phosphatases

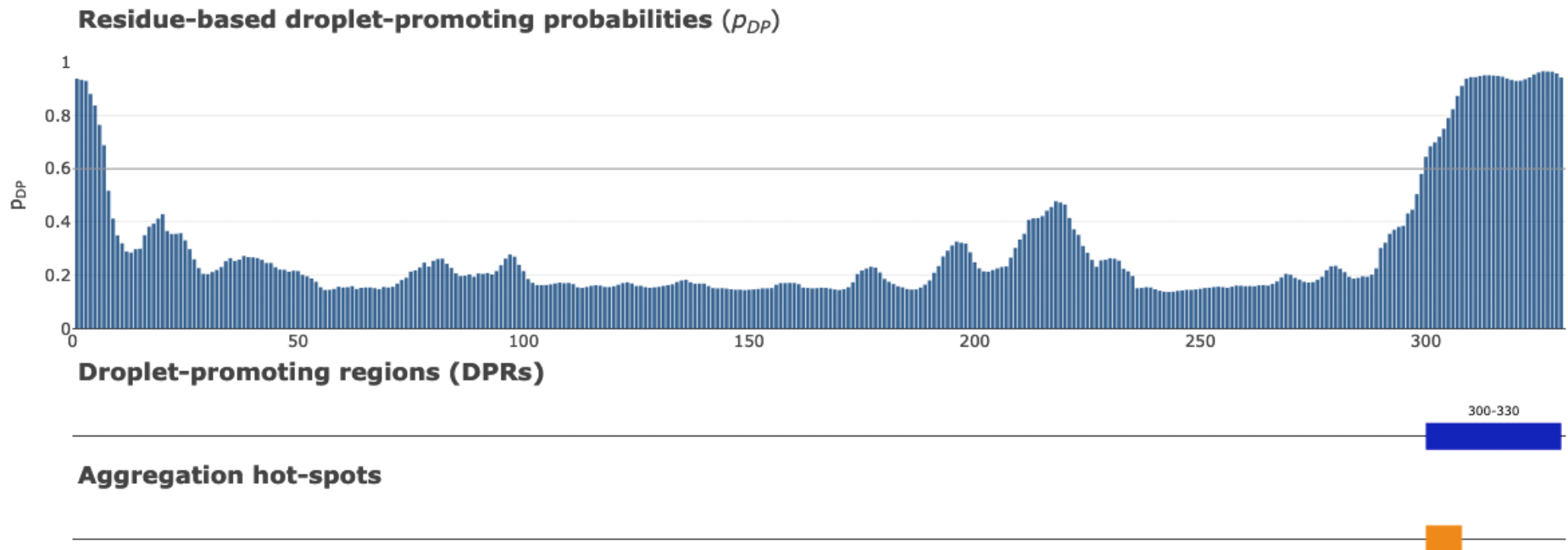
### Pfams:

- [2] Calcineurin-like phosphoesterase
- [3] PB002690 (Pfam-B)
- [4] PB002017 (Pfam-B)
- [5] PB003555 (Pfam-B)

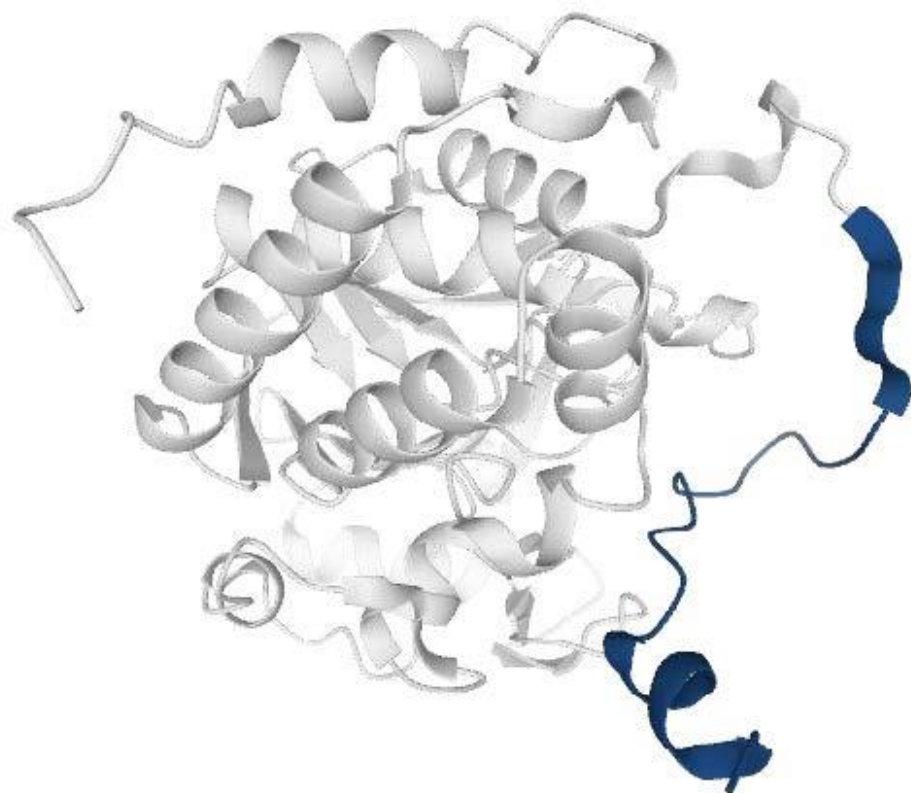
C

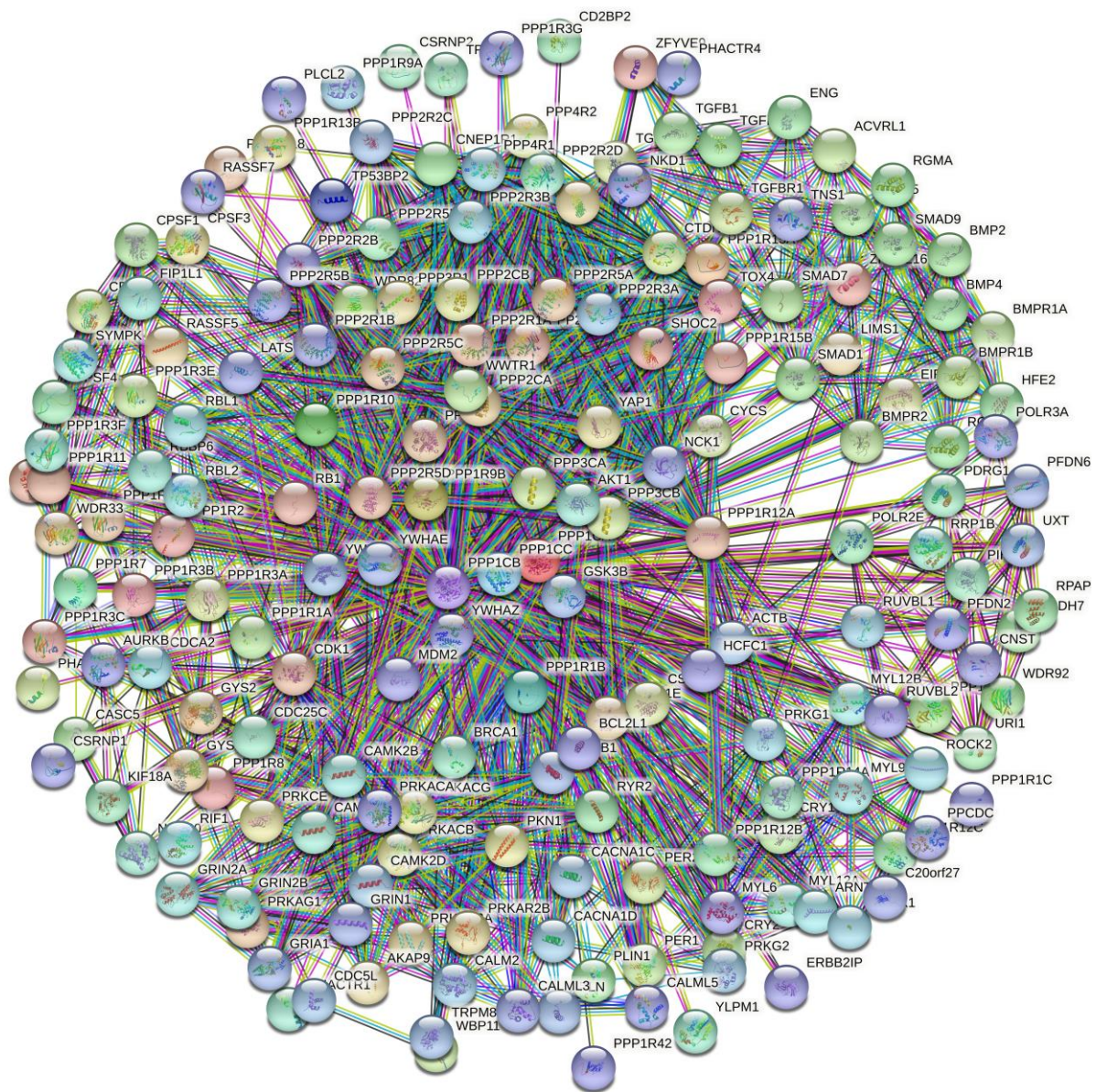
D

Probability of spontaneous liquid-liquid phase separation:  $p_{\text{LLPS}} = 0.1692$



**E**





**F**

minimum required interaction score: high confidence (0.700)

number of nodes: 191

number of edges: 1748

average node degree: 18.3

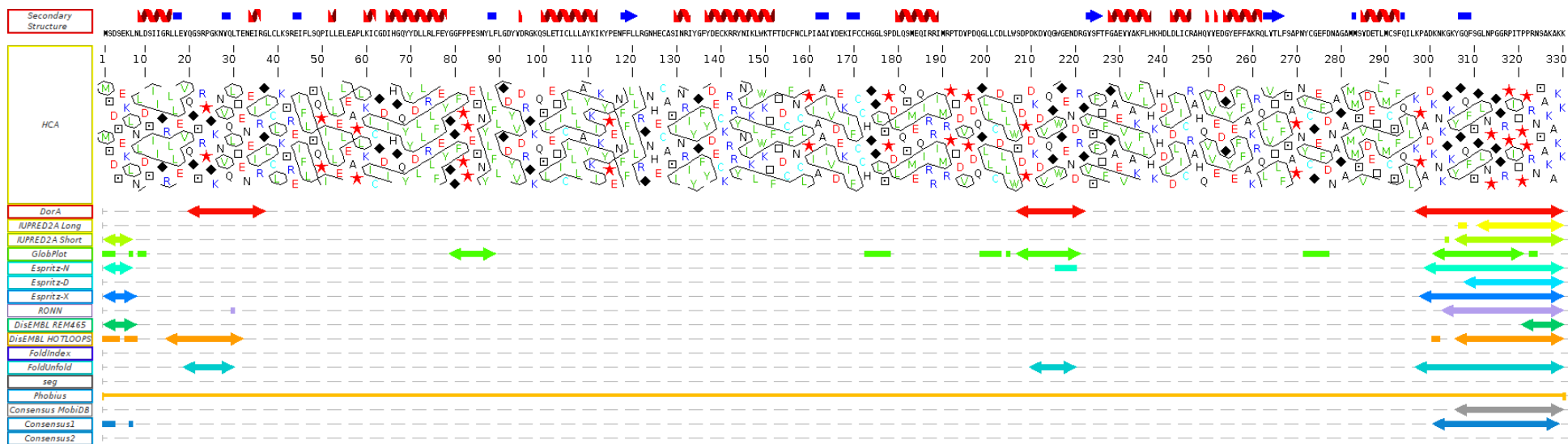
avg. local clustering coefficient: 0.755

expected number of edges: 411

PPI enrichment p-value:  $< 1.0e-16$

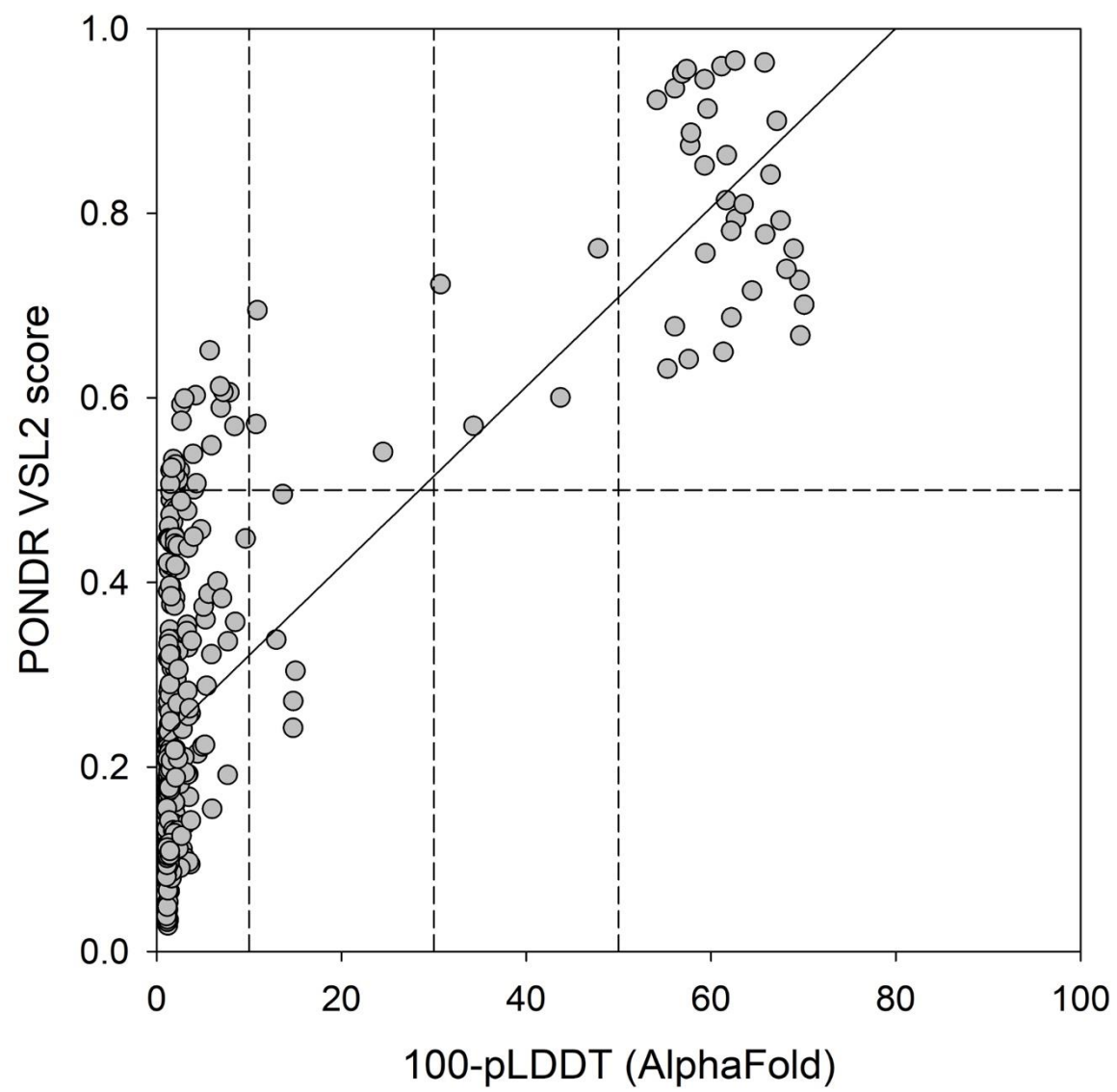


G





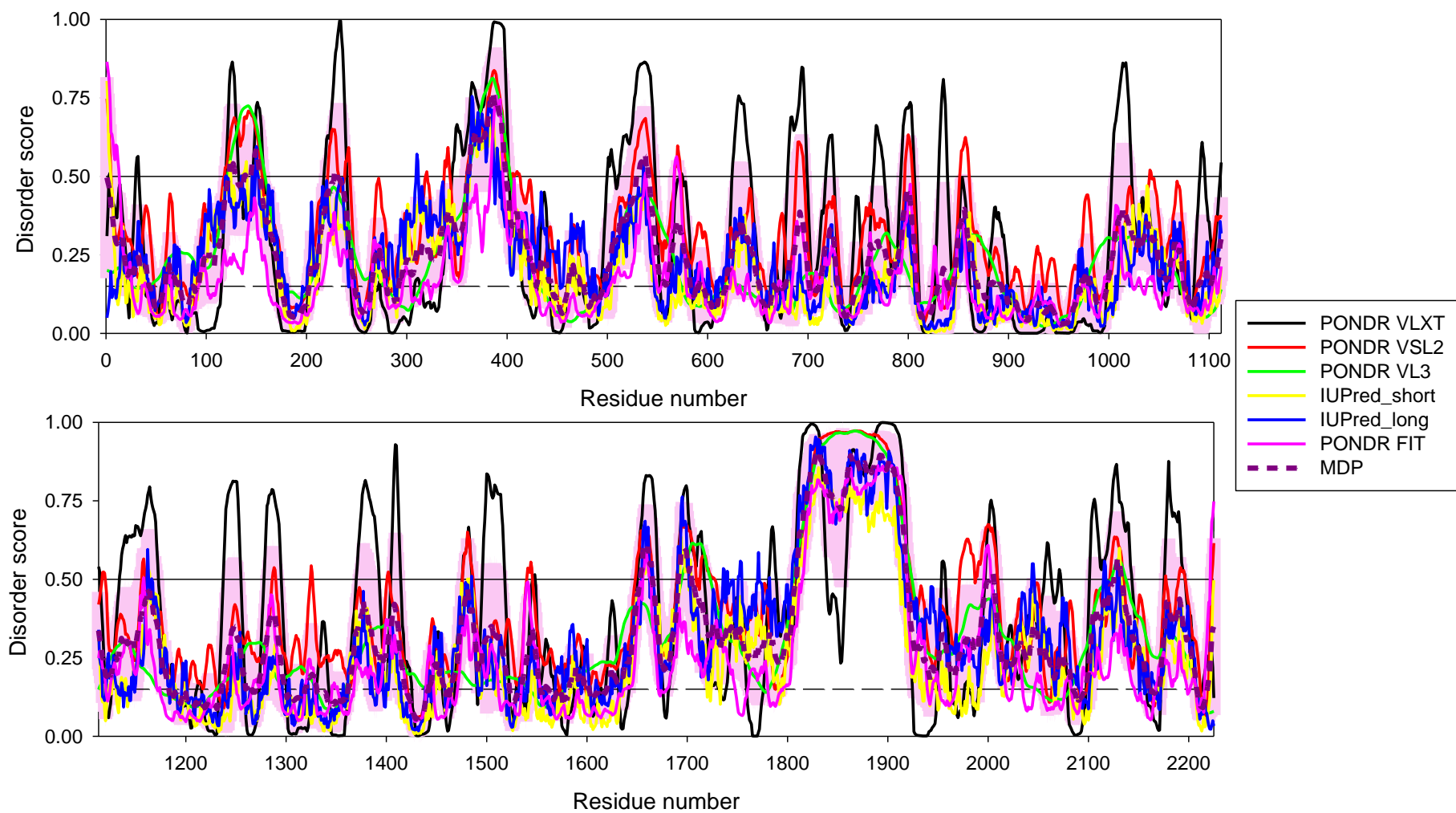
H

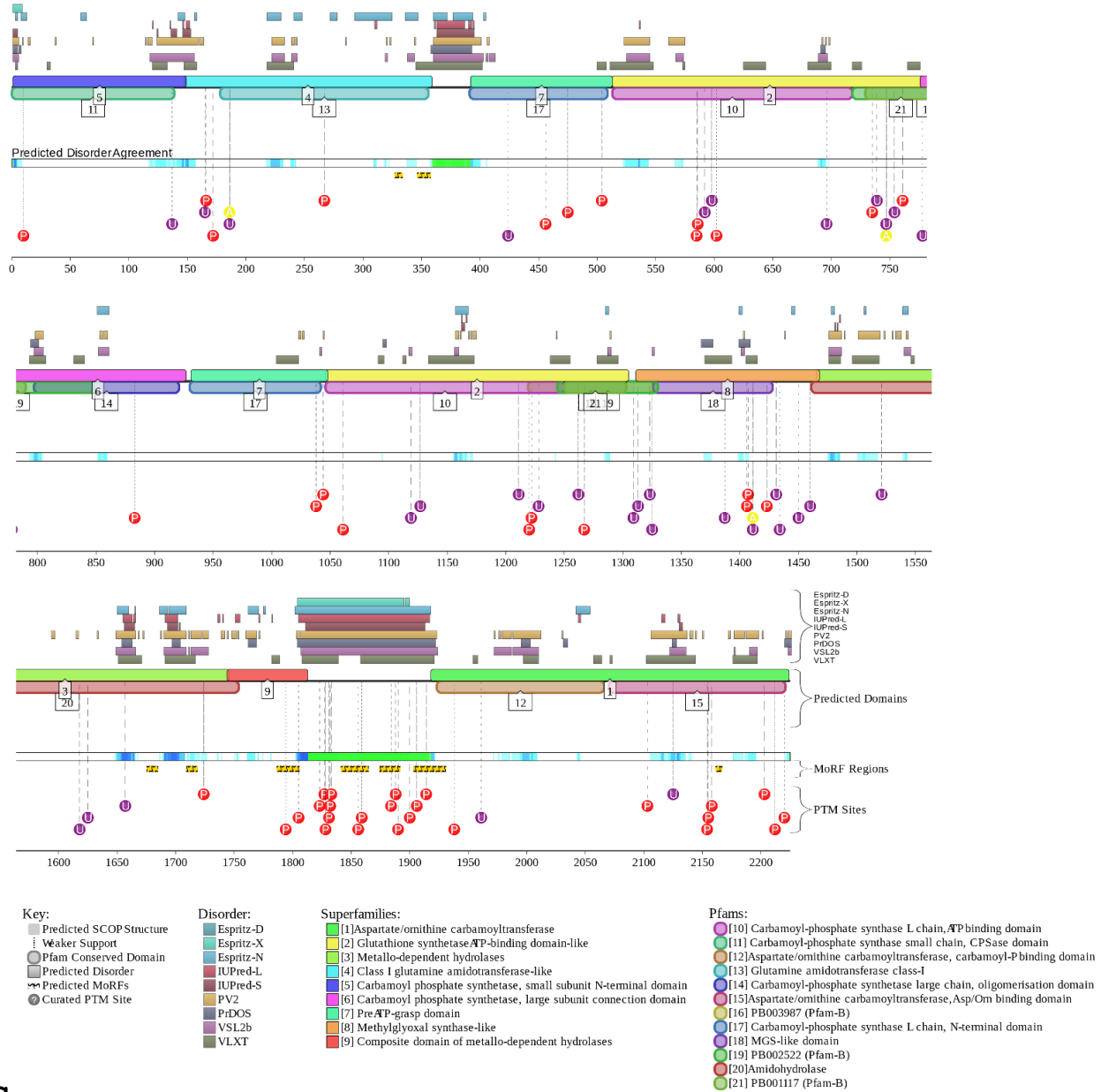


**Supplementary Figure S17.** Functional disorder in CAD protein. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

**A**

```
>sp|P27708|PYR1_HUMAN CAD protein OS=Homo sapiens OX=9606 GN=CAD PE=1 SV=3
MAALVLEDGSVLRGQPFGAAVSTAGEVVFQTMVGYPEALTDPSYKAQILVLTYPLIGNYGIPDEMDEFGLCKWFESSGIHVAALVVGECCPTPSHWSATRTLHEWLQQHGIPLQG
VDTRELTKKLREQGSLLGKLVQNGTEPSSLPFLDPNARPLVPEVSIKTPRVFNTGGAPRILALDCGLKYNQIRCLCQRGAEVTVVPWDHALDSQEYEGFLFLSNGPGDPASYPVSVSTL
SRVLSEPNRPVFGICLGHQLLALAIGAKTYKMRYGNRGHNQPCLLVGSGRCFLTSQNHGFVAVETDSLPAWAPLFTNANDGSNEGIVHNSLPFFSVQFHFPEHQAGPSDMELLFDIFL
ETVKEATAGNPGGQTVRERLTERLCPPGIPTPGSGLPPPRKVLILGSGGLSIGQAGEFDYSGSQAIKALKEENIQTLINPNIAITVQTSQGLADKVYFLPITPHYVTQVIRNERPDGV
LLTFGGQTALNCGVELTKAGVLARYGVRVLGTPVETIELTEDRRAFAARMAEIGEHVAPSEAANSLEQAQAAAERLGPVPLVRAAFALGGLGSGFASNREELSALVAPAFHAITSQVLV
DKSLKGWKEIEYEVVRDAYGNCVTVCNMENLDPLGIHTGESIVVAPSQTLNDREYQLLRQTAIKVTQHLGIVGECNVQYALNPESEQYIIIEVNARLSRSSALASKATGYPLAYVAAK
LALGIPLPELRNSVTGGTAAFEPSVDYCVVKIPRWDLSKFLRVSTKIGSCMKSVGEVMGIGRSFEEAFQKALRMVDENCVGFDHTVKPVSDMELETPTDKRIFVVAALWAGYSVDRL
YELTRIDRWFLHRMKRIIAHAQLLEQHRGQPLPPDLLQQAQKCLGFSKQIALAVLSTELAVRKLRLQELGICPAVKQIDTVAAEWPAQTNYLYLTYWGTTHDLTFRTPHVLVLGSGVYR
IGSSVEFDWCAVGCQQLRKMGYKTIMVNYNPETVSTDYDMCDRLYFDEISFEVMDIYELNPEGVILSMGGQLPNNMAMALHRQQCRVLGTSPEAIDSAENRFKFSRLDITIGISQ
PQWRELSDESARQFCQTVGYPCVVRPSYVLSGAAMNVAYTDGDLERFLSSAAAVSKEHPVVISKFIEAKEIDVDAVASDGVVAAIAISEHVENAGVHSGDATLVTPPQDITAKTLE
RIKAIVHAVGQELQVTGPFNLQLIAKDDQLKVIECNVRVSRSPFVSKTLGVDLVALATRVIMGEEVEPVGLMTGSGVVGKVPQFSFSLAGADVVLGVEMTSTGEVAGFGESRCEA
YLKAMLSTGFKIPKKNILLTIGSYKNKSELLPTVRLLESLSGLYASLGTADFYTEHGKVTAVDWHFEEAVDGECPQRSILEQLAEKNFELVINLSMRGAGGRRLLSSFVTKGYRTR
RLAADFSVPLIIDIKCTKLFVEALGQIGPAPPLKVHVDGMTSQKLVLRLPGLIDVHVHLREPGGTHKEDFASGTAAALAGGITMVCAMPNTRPPIIDAPALALAQKLAEGARCDFALE
LGASSENAGTLGTVAGSAAGLKLYLNETFSELRLDSVVQWMEHFETWPSHLPIVAHAEEQQTVAAVLMVAQLTQRSVHICHVARKEEILLIKAARGPLVPTCEVAPHHLFLSHDDLER
LGPKGGEVRPELGSRDVEALWENMAVIDCFASDHAPHTLEEKCGSRPPPGFPGLETMLPLLLTAVSEGRSLDQLRLHNNPRRIFHLPPQEDTYVEVDLEHEWTIPSHMPFSKAH
WTPFEGQKVKGTVRRVVLRGVAYIDGQVLVPPGYGQDVRKWPQGAVPQLPPSAPATSEMTTTPRPRRGIPGLPDGRFHLPPRIHRASDPGLPAEEPKEKSSRKVAEPELMGTPDGT
CYPPPPVPRQASPQNLGTPGLLHPQTSPLLHSLVGQHILSVQQFTKDQMSHLFNVAHTLRMMVQKERSLDILKGKVMASMFYEVSTRTSSSFAAAMARLGGAVALSFSEATSSVQKGES
LADSVQTMSCYADVVLRLHPQPGAVELAAKHCRPPVINAGDVGGEHPTQALLDIFTIREELGTVNGMTITMVGDLLKHGRTVHSLACLLTQYRVSLRYVAPPSLRMPPTVRAFVASRGT
KQEEFESIEEALPDTDVLYMTRIQRERFGSTQEYEAFCGQFILTIPHIMTRAKKKMVMVHMPMRVNEISVEVSDPDRAAYFRQAENGMYIRMALLATVLGRF
```

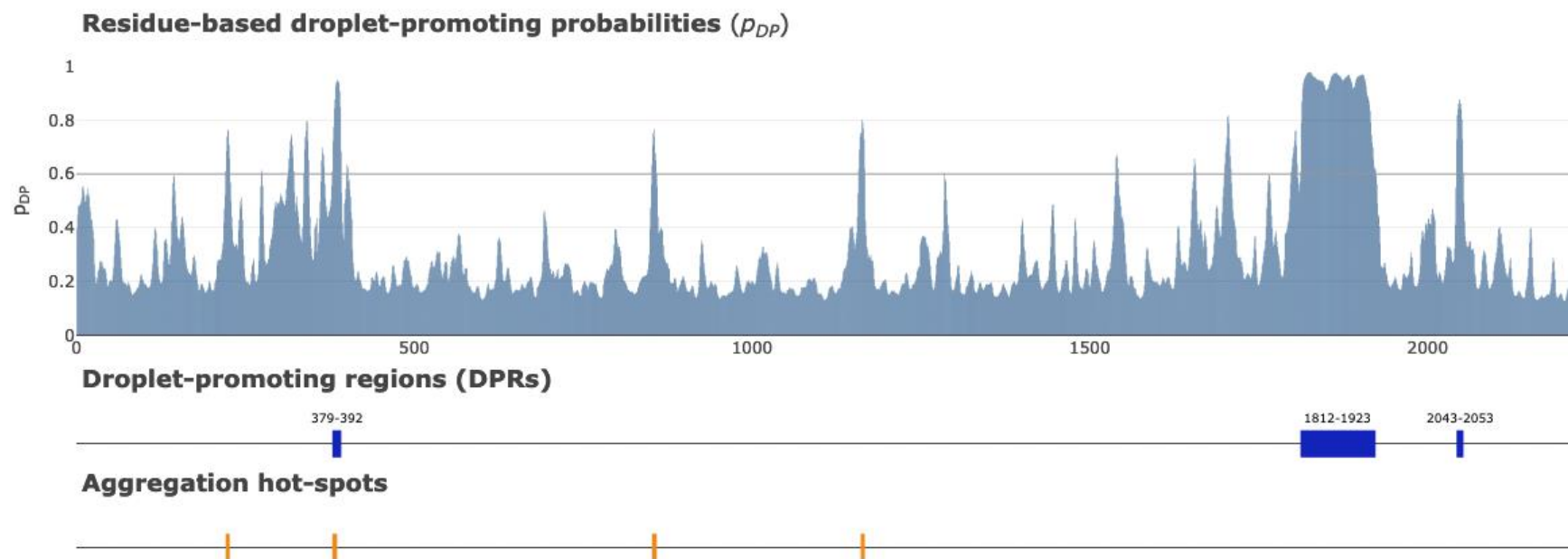
**B**



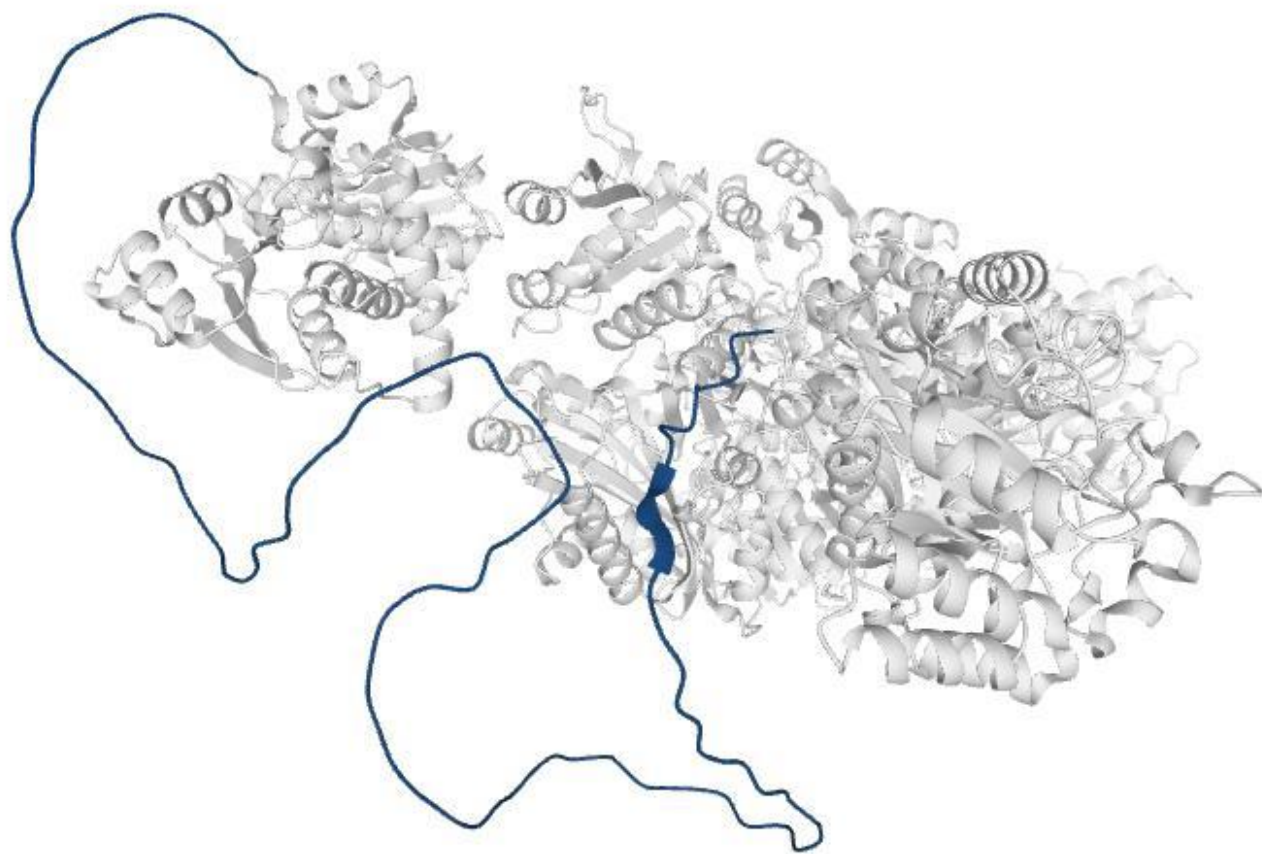
C

D

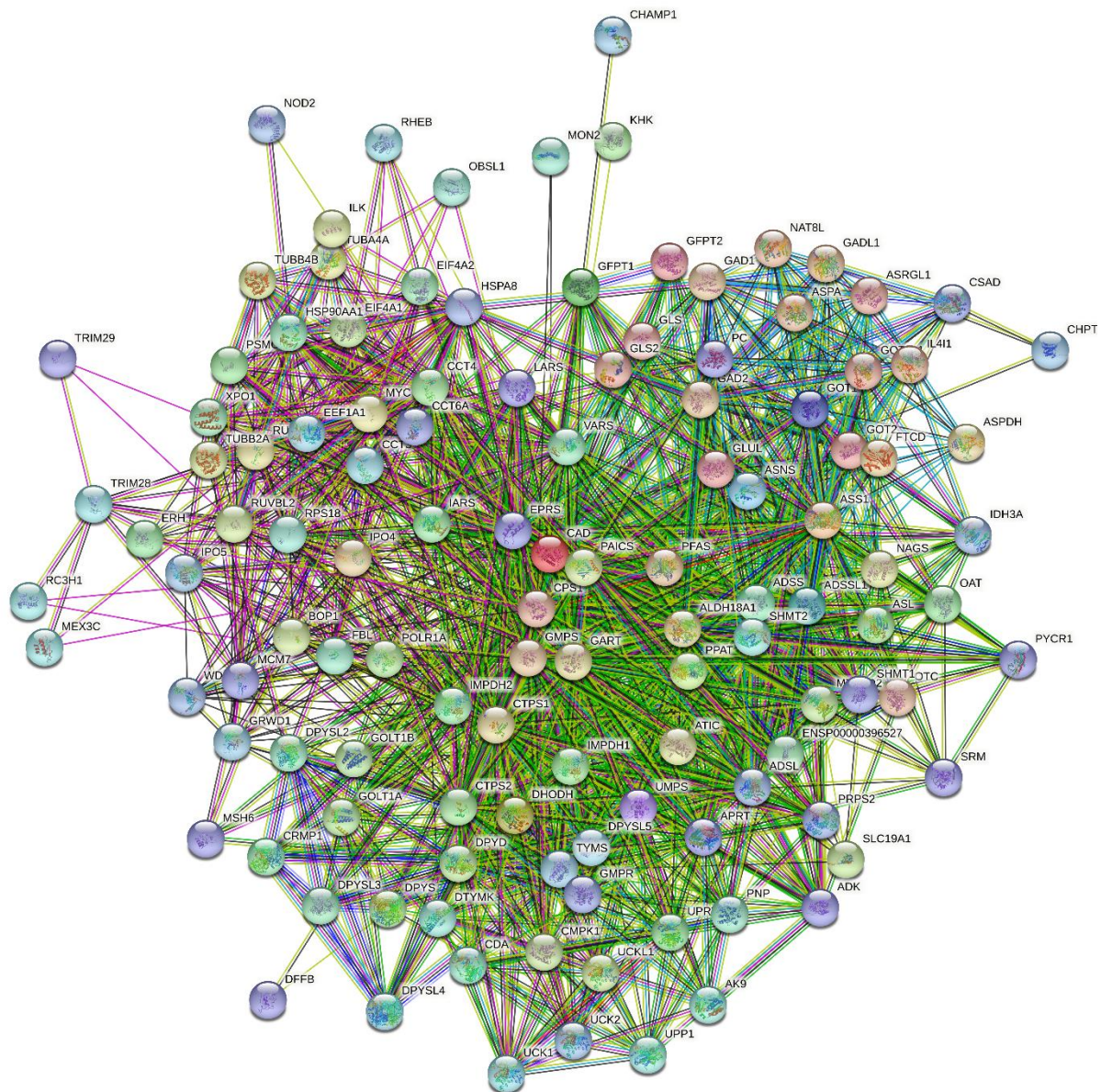
Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.2011$



**E**









minimum required interaction score: medium confidence (0.400)

number of nodes: 119

number of edges: 1358

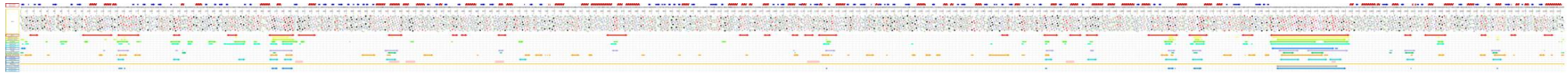
average node degree: 22.8

avg. local clustering coefficient: 0.655

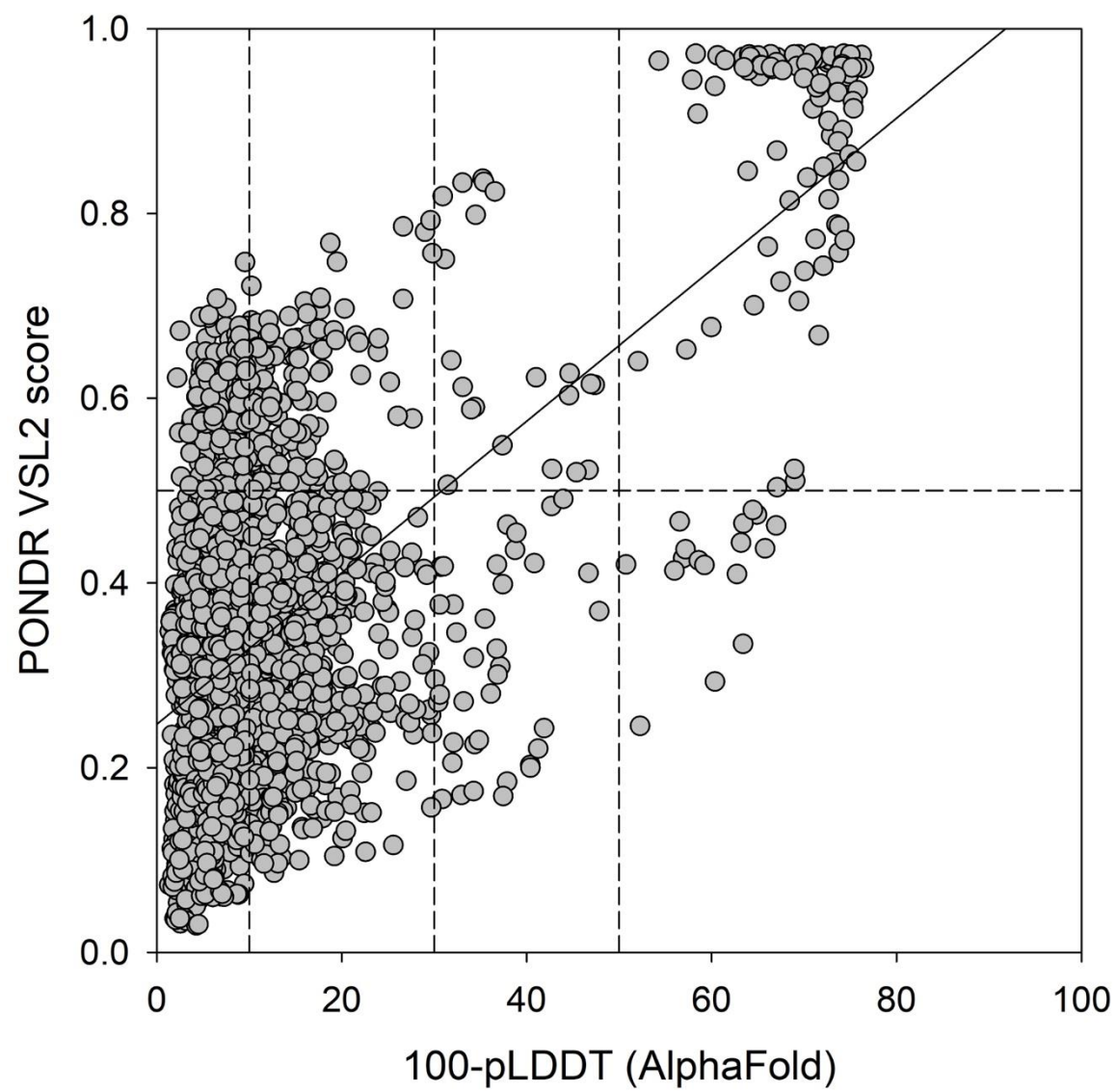
expected number of edges: 325

PPI enrichment p-value:  $< 1.0e-16$

**G**



H

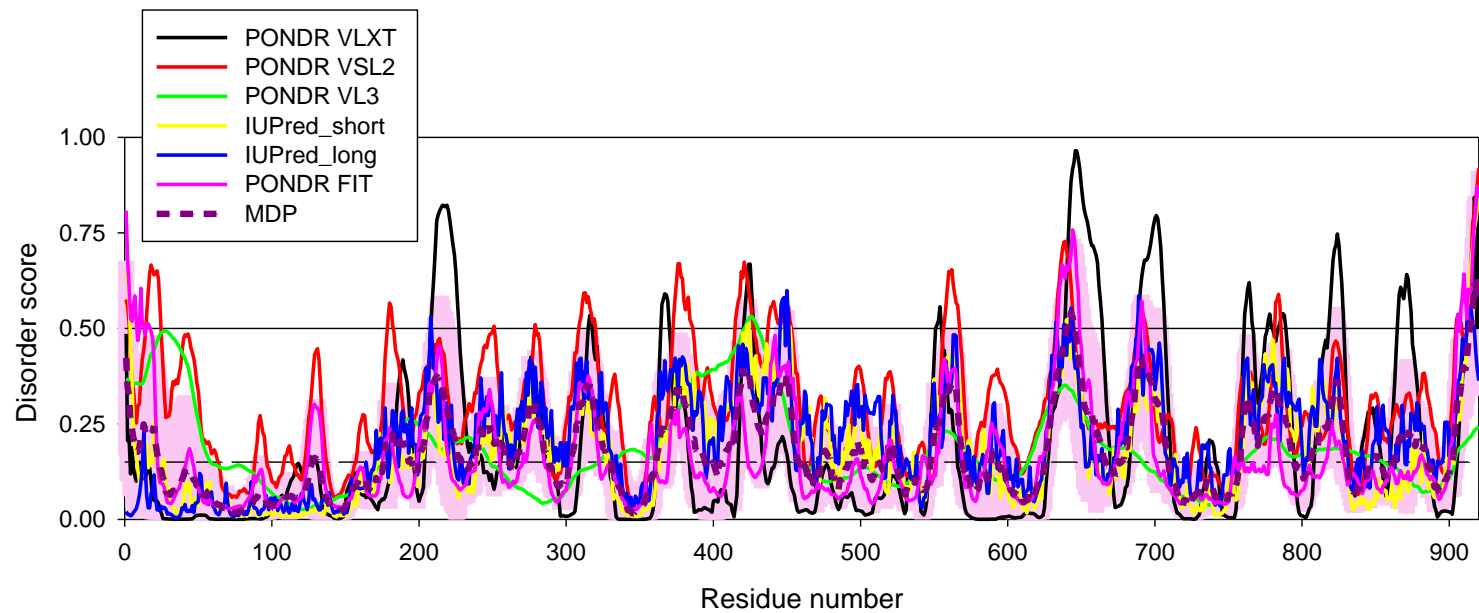


**Supplementary Figure S18.** Functional disorder in UDP-N-acetylglucosamine--peptide N-acetylglucosaminyltransferase 110 kDa subunit. **B.** RIDAO-generated disorder profile. **C.** D2P2-generated functional disorder profile. **D.** FuzDrop output. **E.** AlphaFold2 structure with FuzDrop annotations. **F.** STRING-generated PPI network with corresponding statistics. **G.** MeDor output. **H.** Plot of the per residue disorder score (as provided by PONDR® VLS2) versus (100-pLDDT), where pLDDT is the corresponding AlphaFold2 confidence score.

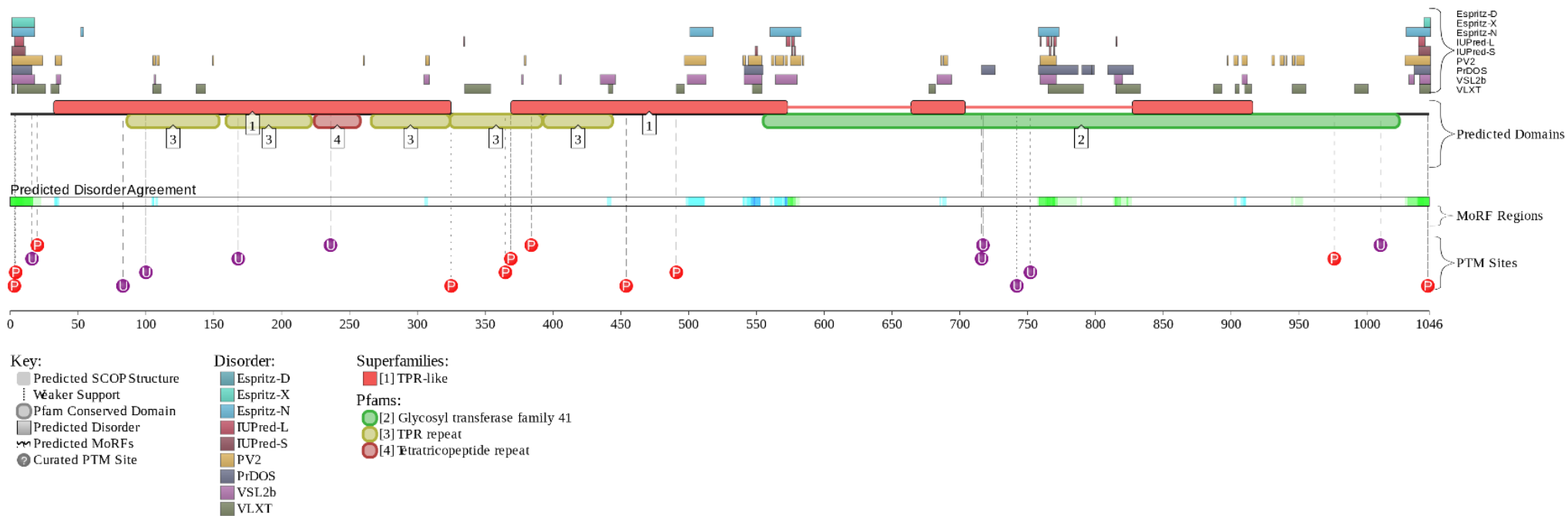
**A**

```
>sp|O15294|OGT1_HUMAN UDP-N-acetylglucosamine--peptide N-acetylglucosaminyltransferase 110 kDa subunit OS=Homo sapiens
OX=9606 GN=OGT PE=1 SV=3
MASSVGNVADSTEPTKRMLS FQGLAELAHREYQAGDFEAAERHCMQLWRQEPDNTGVLLLLSSIH FQCRR LDRSAHFSTLAIKQNPLLA EAYSNLGNVYKERGQLQE AIEHYRHALRL
KPDFIDGYINLAAALVAAGDMEGAVQAYVSALQYNPDLYCVRSDLG NLLKALGRLEEAKACYLKAIETQPNFAVAWSNLGCVFNAQGEIWLAIHHFEKAVTLDPNFLDAYINLGNVLK
EARIFDRAVAAYLRALSLSPNHAVVHG NLA CVVYEQGLIDLAI DTYRR AIELQPHFPDAYCNLANALKEKGSVAEAE DCYNTALRLCPTHADSLNNLANIKREQGNIEEAVRLYRKAL
EVFPEFAAAHSNLASVLQQQ GKLQEALMHYKEAIRISPTFADAYS NMGN TLKEMQDVQ GALQCYTRAIQINPAFADAHSNLASIHKDSGNIPEAIAS YRTALKLKPDPDPDAYCNLAHC
LQIVCDWTDYDERMKKLVSI VADQLEKNRLPSVHPHSM LYP LSHGFRKAIAERHG NLC LDKINVLHKKPPYEH PKDLKLS DGR LRVGYVSSDFGNHPTSHLMQSI PGMHNPDKFEVFC
YALSPDDGTNFRVKVMAE ANHFIDLSQIPCNGKAADRIHQDGIHILVNMNGYTKGARNELFALRPAPIQAMWLGYPGTSGALFMDYIITDQETSPA EVAEQYSEKLAYMPHTFFIGDH
ANMFPHLKKKAVIDFKSNGHIYDNRIVLNGIDLKAF LDSL PDVKIVKMKCPDGGDNADSSNTALNMPVIPMNTIAEAVIEMINRGQIQITINGFSISNGLATTQINNKAATGEEVPRT
IIVTTRSQYGLPEDAIVYCNFNQLYKIDPSTLQMWANILKRV PNSVLWLLRFP AVGEPNIQQYAQNMG L PQNR IIFSPVAPKEEHVRRGQLADVCLDTPLCNGHTTGMDVLWAGTPMV
TMPGETLASRVAASQLTCLG CLELIAKNRQEYEDIAVKLGTDLEYLKKVRGKVWKQR ISSPLFNTKQYTMELERLYLQMWEHYAAGNKPDHMIKPVEVTESA
```

**B**

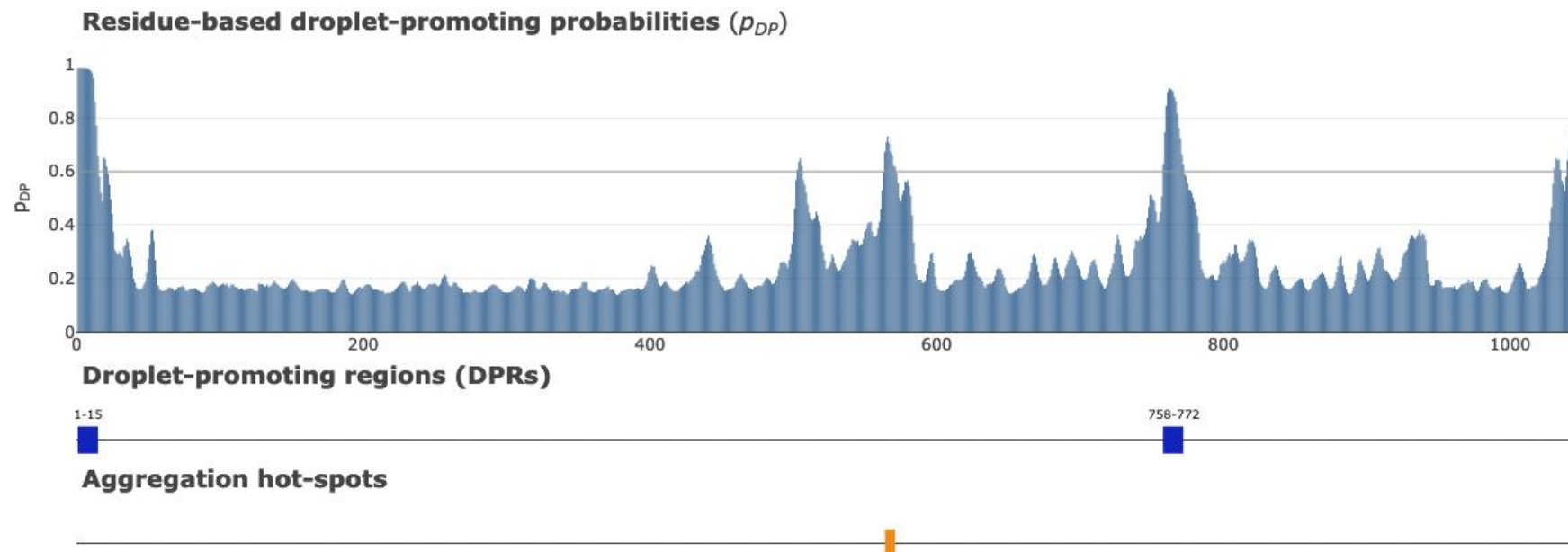


C



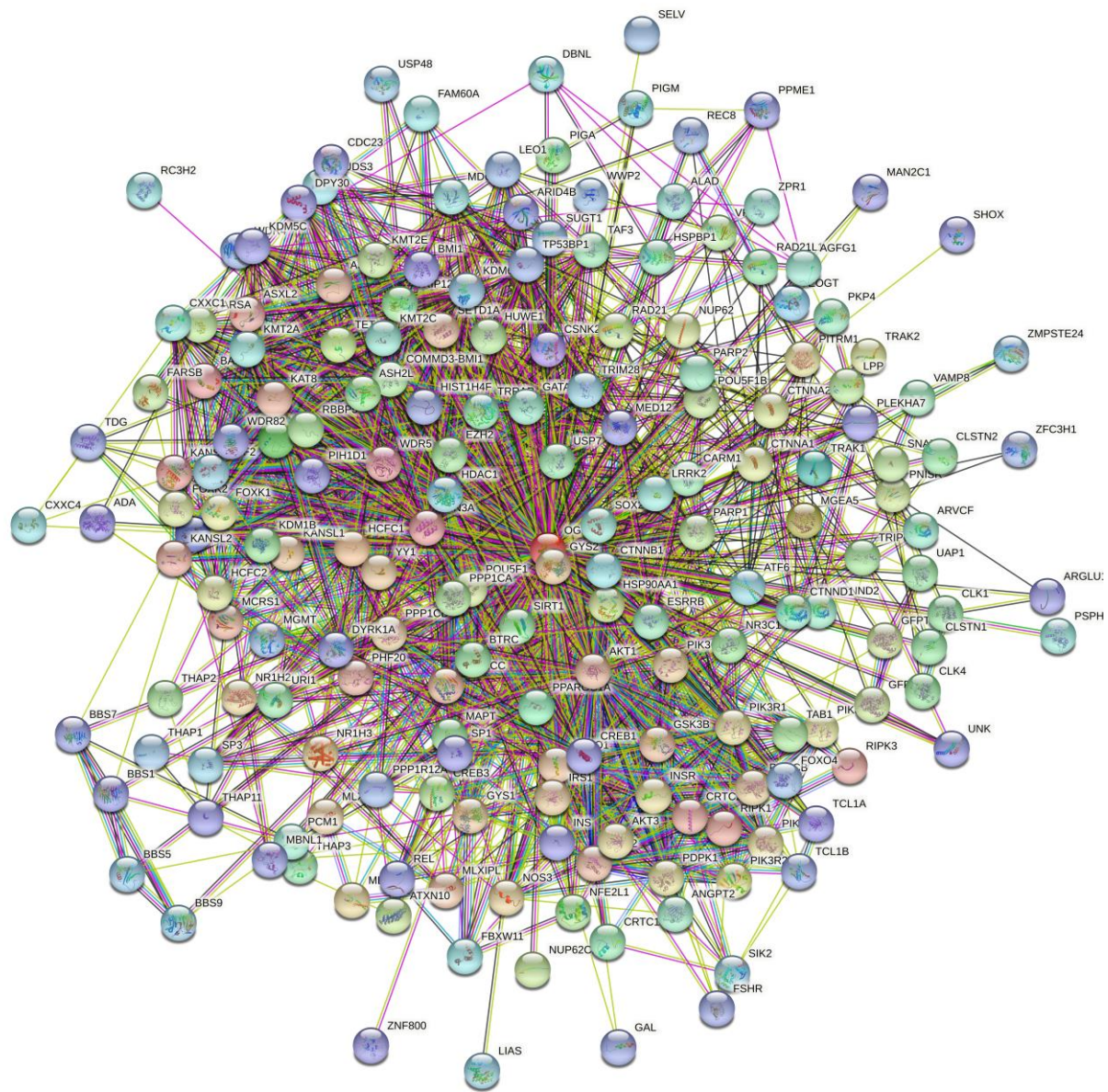
**D**

Probability of spontaneous liquid-liquid phase separation:  $p_{LLPS} = 0.1567$



**E**

There is no Alpha-Fold-generated 3D structure of this protein in FuzDrop.



**F**



minimum required interaction score: medium confidence (0.400)

number of nodes: 189

number of edges: 1609

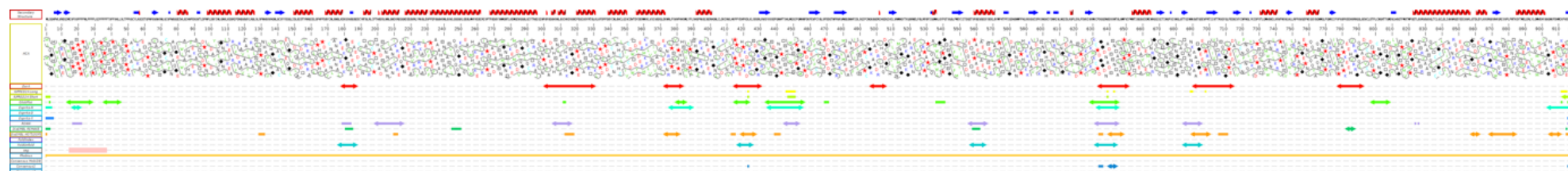
average node degree: 17

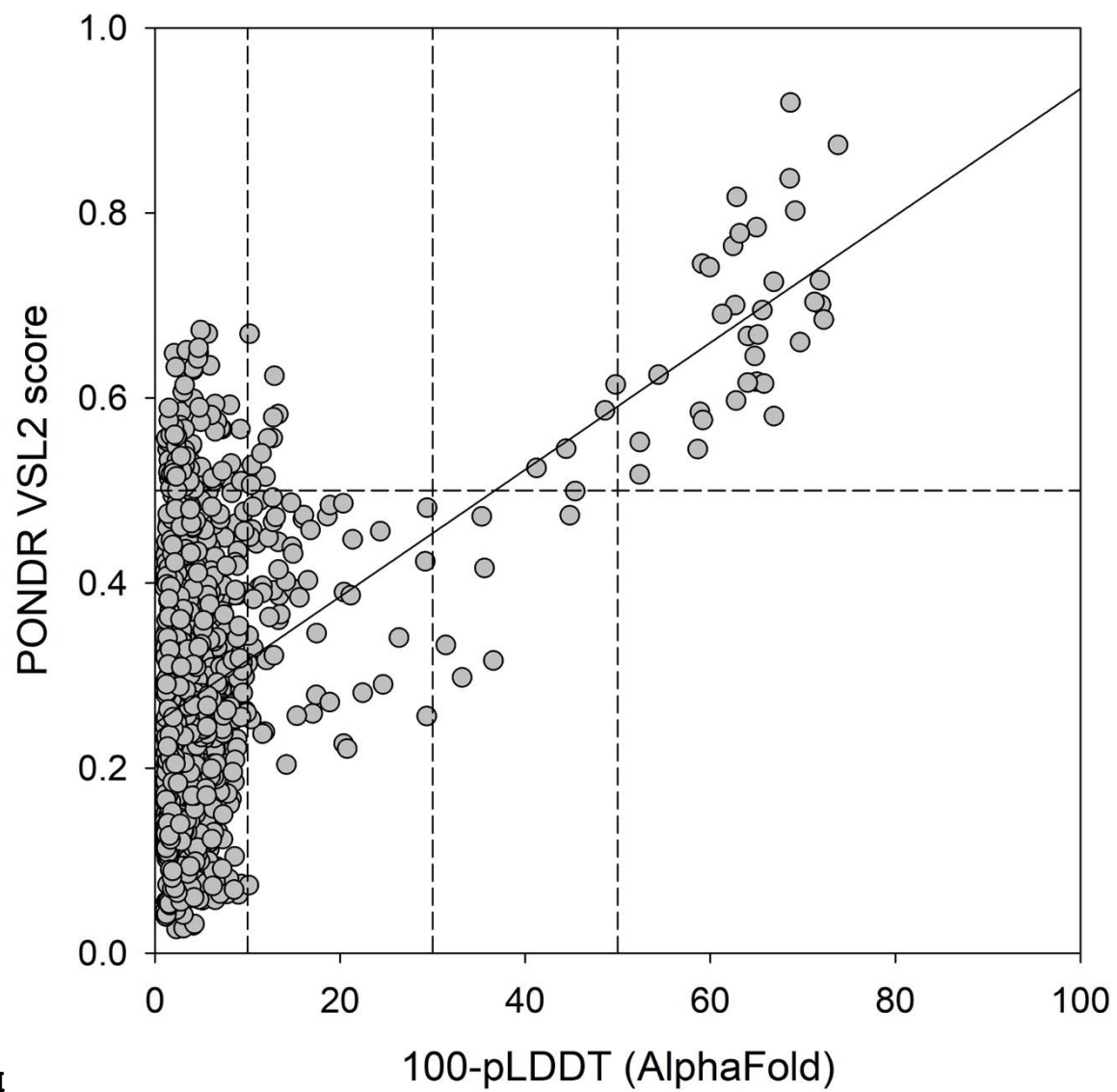
avg. local clustering coefficient: 0.617

expected number of edges: 716

PPI enrichment p-value:  $< 1.0e-16$

G





H