Physico-chemical property	Reference domains from PFAM
Nucleic Acid Binding-interface_close-1 (Terribilini *et al.*, 2006)	SEC13_HUMAN/202-244,RBBP5_HUMAN/15-52, E9PB61_HUMAN/115-184, APAF_HUMAN/647-685
Nucleic Acid Binding-HB (Lewis *et al.*, 2011) Nucleic Acid Binding-interface (Lewis *et al.*, 2011) Nucleic Acid Binding-interface_close+1 (Terribilini *et al.*, 2006)	SEC13_HUMAN/3-41,PELO_HUMAN/271-370, GAR1_HUMAN/46-203,SRSF6_HUMAN/112-206 SF3A2_HUMAN/41-91,CELF1_HUMAN/403-473, A0A024R4E5_HUMAN/586-637
Aggregation (Pawar *et al.*, 2005)	H0YAS6_HUMAN/76-147, CELF1_HUMAN/124-186, SURF6_HUMAN/135-351,U3IP2_HUMAN/231-269,
Aggregation (Conchillo-Solé *et al*., 2007) Aggregation med (Fernandez-Escamilla *et al.*, 2004) Aggregation high (Fernandez-Escamilla *et al.*, 2004)	FAKD1_HUMAN/779-838, NOP58_HUMAN/253-401, WDHD1_HUMAN/3-41, APAF_HUMAN/1075-1113, RBM4_HUMAN/160-177,ZCH14_HUMAN/906-923, RBM4_HUMAN/160-177,ENSP00000361327_13-214, MAZ_HUMAN/438-488, LN28B_HUMAN/127-144
Hydrophobicity (Sweet and Eisenberg, 1983) Hydrophobicity (Bull and Breese, 1974) Hydrophobicity (Abraham and Leo, 1987) Hydrophobicity (Black and Mould, 1991) Hydrophobicity (Fauchere and Pliska, 1983) Membrane-buried preference (Argos *et al.*, 1982) Transmembrane regions (Nakashima *et al.*, 1990)	XRCC6_HUMAN/558-607, WDR1_HUMAN/224-262 PLRG1_HUMAN/403-440, ZCH14_HUMAN/906-923 ENSP00000361327_13-214 NOP58_HUMAN/253-401, NOP58_HUMAN/253-401, XRCC6_HUMAN/558-607 PI3R4_HUMAN/983-1021, HTSF1_HUMAN/291-347 TBL3_HUMAN/282-320
Normalized frequency of alpha-helix (Levitt, 1978) Normalized frequency of alpha-helix (Burgess *et al.*, 1974) Normalized frequency of middle helix (Crawford *et al.*, 1973) Average relative probability of helix (Kanehisa and Tsong, 1980) Normalized frequency of alpha-helix (Palau *et al.*, 1982) Normalized frequency of beta-sheet (Chou and Fasman, 1978) Normalized frequency of beta-sheet (Crawford *et al.*, 1973) Average probability of inner beta-sheet (Kanehisa and Tsong, 1980) Normalized frequency of beta-sheet (Levitt, 1978)	GAR1_HUMAN/46-203 SRSF6_HUMAN/112-206 PRP8_HUMAN/1208-1343 PELO_HUMAN/271-370 DCAF8_HUMAN/226-266 KTNB1_HUMAN/221-258 RL5_HUMAN/26-173, CSTF1_HUMAN/387-425 FUS_HUMAN/287-365 RB15B_HUMAN/420-482, TAF5L_HUMAN/259-296
Normalized frequency of coil (Nagano, 1973) TOP-IDB (Campen *et al.*, 2008) Average flexibility indices (Bhaskaran and Ponnuswamy, 1984) UnfoldOverFold (Campen *et al.*, 2008) Coil (Deléage and Roux, 1987) Proportion of residues 95% buried (Chothia, 1976) Percentage of buried residues (Janin and Wodak, 1978) Energy transfer from out to in (95% buried) (Radzicka *et al.*, 1988)	NCBP2_HUMAN/56-116 SUV3_HUMAN/624-674, MINT_HUMAN/519-583 FAN_HUMAN/704-740 LN28B_HUMAN/149-166 GAR1_HUMAN/46-203 XRCC6_HUMAN/558-607, APAF_HUMAN/1034-1071 RBM4_HUMAN/160-177, RBM4_HUMAN/160-177 TBL3_HUMAN/567-591, ZFR_HUMAN/369-419

Physico-chemical properties and RNA-binding domains used to discriminate RBPs and RNA-binding regions. The domain sequences have been taken from PFAM database and filtered by sequence similarity. To explain annotations with an example, CELF1_HUMAN/403-473 indicates the RRM domain located at amino acids 403-473 of protein CELF1, which is associated with 'nucleic acid binding' property taken from a previous publication (Terribilini *et al.*, 2006).

In addition to RNA-binding propensities, we found that structural disorder, aggregation and membrane domains are key-characteristics to determine protein ability to interact with transcripts, followed by secondary structure propensities:

- Structural disorder (Castello *et al.*, 2012) is intrinsically associated with low burial and large radius of gyration (Marsh, 2013);
- Strong hydrophobicity was found in the RDs of RBPs that are intrinsically prone to aggregate: a study investigating truncated constructs of TDP43 in yeast, reports that presence of the RRM2 is necessary for amyloid fibrils formation (Johnson *et al.*, 2008);
- A number of membrane proteins associate with RNA to control viral replication (Hyodo *et al.*, 2014; Sha and Luo, 1997)
- Secondary structure is a key signature of known RDs and defines the affinity for RNA-binding (Lunde *et al.*, 2007; Maris *et al.*, 2005);