Figure S1 Multiple sequence alignment of PAZ domains.

	1	2	1	2	2	
		2				0 000000
	10 20	20		X X 60 X	70 X	80
Dm Ago2 Q9VUQ5	SMPMIEYLERFSLKAKIN-NT-	TNL-DYSERFLEPFLEG	INVVYTPPOSFOS			GKKVTIASYFHS
	AQPVIDFMCEVLDIRDINEOR-	<mark>KPLTD</mark> SQRVKFTKEIKG			R <mark>P</mark> AQMQ <mark>SFP</mark> LQLEN <mark>G</mark>	TVECTVAKYFLD
At AGO1 004379	ANPVIQFVCDLLNRDISS	RPLSDADRVKIKKALRG			VATRELTFPVDER	NTQKSVVEYFHE
Hs IF2C1 Q9UL18	AQPVIEFMCEVLDIRNIDEQP-	<mark>KPLTD</mark> SQRVR <mark>F</mark> TKEIKG	LKVEVTHCGQMK-	RKYRVCNVTRI	R <mark>P</mark> ASHQTFPLQLESGC	TVECTVAOYFKO
Sp_IF2C_074957	NDSLLQILMEYTDCSNV	<mark>RDLT</mark> RFDLKRLSRKFRF	LKVTCQHRNNVGT	DLANRVYSIEGFSSI	KSASDSFFVRRLNG	EEQKI <mark>SVAEYF</mark> LE
Ce_RDE-1_Q9XU82	KMSLLDYLLLIVDPQSCNDDV [1	2] MTIRQAAR <mark>P</mark> RIRQLLEN	LK <mark>L</mark> KCAEVWD <mark>N</mark> EMSR	-LTERHLTFLDLCEN	EN <mark>S</mark> LVYK <mark>VT</mark> GKSDRGF	NAKKYDT <mark>TLFKIYEE</mark>
At_Zwille_Q9XGW1	PLPVIEFVAQLLGKDVLS	<mark>KPLSD</mark> SDRVK <mark>I</mark> KK <mark>GL</mark> RG	<mark>vkvevth</mark> ranvr-	RKYRVAGLTT(QPTRELMFPVDEN	CTMK <mark>SVIEY</mark> FQE
Dm_PIWI_Q9VKM1	TETIYDIMRRCSHNP	ARHQDE <mark>V</mark> RVN <mark>V</mark> LD	LIVLTDYNN	RTYRINDVDF	GQTPKSTFSCK	<mark>G</mark> RDI <mark>SFVEYY</mark> LT
Dm_STING_076922	TETLYNILSDAIRDS	<mark>D</mark> DYQST <mark>F</mark> KRA <mark>V</mark> MG	MVILTDYNN	KTYRIDDVDF(QS <mark>TP</mark> LCKFKTND	<mark>G</mark> EI <mark>SYV</mark> DYYKK
Hs_DICER_Q9UPY3	DFK <mark>FME</mark> DIEKSEARIGIPST	KYTKET <mark>P</mark> F <mark>V</mark> FKLEDY	QDAVII <mark>P</mark> RYR <mark>N</mark> FDQ-	<mark>P</mark> HRFYVADVYTI	D <mark>LTP</mark> LSK <mark>FP</mark> S	<mark>P</mark> EYE <mark>TFAEYY</mark> KT
Dm_DICER_Q9VCU9	DWQFLELIQANGNTMPRAVP	DE <mark>E</mark> RQAQ <mark>PF</mark> D <mark>P</mark> QR-F				NYR <mark>TF</mark> KH <mark>YY</mark> LV
At_CAF_Q9SP32	LL <mark>PV</mark> RDAFEKEVEEDLSKGK	<mark>L</mark> MMAD <mark>G</mark> CMVAEDLIG	KI <mark>VTA</mark> A <mark>H</mark> S <mark>G</mark>	<mark>KRFYV</mark> DSICYI	D <mark>MS</mark> AET <mark>SFP</mark> RK <mark>EG</mark> YL <mark>C</mark>	<mark>P</mark> LEYN <mark>TYA</mark> DYYKQ
	· · · -			• • •	: .	
	000 0 0000			• • • • • • • •		
					130	140
Dm_Ago2_Q9VUQ5			KS	110 X 120	130 ALN <mark>RK</mark> DGATQVANMI	140 YAATS
Dm_Ago2_Q9VUQ5 Dm_AGO1_Q9V6V6	90 100		К <mark>Н</mark>	110 X 120		
	90 100 R-NYPLKFPQLHCLNVGSSI		K <mark>H</mark> RP	110 X 120 ILLPIELCSIEEGO TYLPLEVCNIVAGO NYLPMEVCKIVEGO	ALN <mark>RKDG</mark> ATOVANMI RCIKKLTDMOTSTMI RYSKRLNEROITALLF	ATARS
Dm_AGO1_Q9V6V6	90 100 R-NYPLKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH		K <mark>H</mark> R <mark>P</mark> KH	110 X 120 ILLPIELCSIEEG02 TYLPLEVCNIVAG0 NYLPMEVCKIVEG0 TYLPLEVCNIVAG0	ALN <mark>RKDG</mark> ATOVANMIP RCIKKLTDMOTSTMIP RYSKRLNEROITALLP RCIKKLTDNOTSTMIP	ATARS VTCQR ATARS
Dm_AGO1_Q9V6V6 At_AGO1_004379	90 100 R-NYPLKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH TYGFRIQHTQLPCLQVGNSN		K <mark>H</mark> R <mark>P</mark> KH	110 X 120 ILLPIELCSIEEG02 TYLPLEVCNIVAG0 NYLPMEVCKIVEG0 TYLPLEVCNIVAG0	ALN <mark>RKDG</mark> ATOVANMIP RCIKKLTDMOTSTMIP RYSKRLNEROITALLP RCIKKLTDNOTSTMIP	ATARS VTCQR ATARS
Dm_AGO1_09V6V6 At_AGO1_004379 Hs_IF2C1_09UL18	90 100 R-NYP LKFPQLHCLNVGSSI KYRMKLRYPHPCLQVGQEH TYGFRIQHPQLPCLQVGNSN KYNLQLKYPHPCLQVGQEQ		KH R <mark>P</mark> KH	110 X 120 ILLPIELCSIEEGQ TYLPLEVCNIVAGO NYLPMEVCKIVEGO TYLPLEVCNIVAGO AMLPIEFCFVVKGO	ALN <mark>RKDG</mark> ATOVANMIP RCIKKLTDMOTSTMIP RYSKRLNEROITALLP RCIKKLTDNOTSTMIP	ATARS VTCQR ATARS FAVQR
Dm_AGO1_09V6V6 At_AGO1_004379 Hs_IF2C1_09UL18 Sp_IF2C_074957	90 100 R-NYPLKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH KYRLQLKYPHLPCLQVGQEQ NHVRLQYPHLPCLQVGQEQ NHVRLQYPHLPCLUVKNG N-KKFIEPPHLPLVKVKSGA MYGFTIQHTHLPCLQVGNQK		KH 	110 X 120 ILLPIELCSIEEGO TYLPLEVCNIVAGO TYLPLEVCNIVAGO TYLPLEVCNIVAGO AMLPIEFCFVVKGG SYLPMEALEVHEKP SYLPMEACKIVEGO	ALN <mark>RKOG</mark> ATOVANNI F RCIKKLTDMOTSTMI F RYSKRLNEROITALLF RCIKKLTDNOTSTMI F RYTAKLNSDOTANNI F DRVKNRIDLVMODKFI RYTKRLNEKQITALLF	KATARS KVTCQR KATARS RFAVQR KRATR KVTCQR
Dm_AG01_Q9V6V6 At_AG01_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XGW1 Dm_PIWI_Q9VKM1	90 100 F-NYPLKFPQLHCLNVGSSI KYRMKLRYPHPCLQVGQEH KYRLQLKYPHPCLQVGNSN KYNLQLKYPHPCLQVGQEQ NHVRLQYPNLPCILVKNG N-KKFIEFPHLPLVKVKSGA MYGFTIQHHLPCLQVGNQK KYNIRDHNQPLLISKNR		KH KH KE KE KALKTNASEL	110 X 120 ILLPIELCSIEEGO TYLPLEVCNIVAGO NYLPMEVCNIVAGO TYLPLEVCNIVAGO AMLPIEFCFVVKGQ YAVPMEHLEVHEKPC SYLPMEACKIVEGO VVLIPELCRVTGLN2	ALNRKOGATOVANNI RCIKKLTDMOTSTMI RTSKRLNEROITALL RCIKKLTDNOTSTMI RYMAKLNSDOTANNI RYMKLNSDOTANNI RYMKLNEKQITALL AEMRSNFQLMRAMSSY	KATARS KVTCQR KATARS KFAVQR KRATR KVTCQR TRMN <mark>P</mark>
Dm_AG01_Q9V6V6 At_AG01_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XW81 Dm_PIWI_Q9VKM1 Dm_STING_076922	90 100 R-NYPLKFPQLHCLNVG SSI KYRMKLRYPHLPCLQVGQEH TYGFRIQHTQLPCLQVGNSN KYNLQLKXPHLPCLQVGQEQ NHNVRLQYPNLPCILVKNG N-KKFIEFPHLPLVKVKSGA MYGFTIQHTHLPCLQVGNQK RYNIRIRPHNQPLLISKNR RYNIIIRDLKQPLVMSRP		KH KH KE KE KALKTNASEL DKALKTNASEL DKNIRGGNDQA	110 X 120 ILLPIELCSIEEGO TYLPLEVCNIVAGO NYLPMEVCKIVEGO TYLPLEVCNIVAGO AMLPIEFCFVVKGO YAVPMEHLEVHEKP SYLPMEACKIVEGO VVLIPELCRVTGLN IMIIPELARATGMT	ALNRKDGÄTOVANNI RCIKKLTDMOTSTMIF RYSKRLNEROITALLF RYTAKLNSDOTANNI RYTAKLNSDOTANNI RYKNRIDLVMQDKFI RYKKRLNEKOITAL AEMRSNFQLMRAMSSY DAMRADFRTLRAMSEH	ATARS VVTCQR ATARS FRAVQR KRATR VVTCQR TRMNP TRMNP
Dm_AG01_Q9V6V6 At_AG01_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XGW1 Dm_PIWI_Q9VKM1 Dm_STING_076922 Hs_DICER_Q9UPY3	90 100 R-NYPLKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH KYRLQLKYPHLPCLQVGQEQ KYNLQLKYPHLPCLQVGQEQ NHVRLQYPHLPCLUVGNG N-KKFIEFPHLPLVKVKSGA MYGFTIQHTHLPCLQVGNQK KYNIRIRDHNQPLLISKNR RYNIIIRDLKQPLNSRPT RYNLIRDKQPLLDVDHTSSRI	NLLTPRHLNQKGKALPLS		110 X 110 X 120 111 DFELCSIEGO 111 DFELCSIEGO 111 DFELCSIEGO 112 DFECSURACI 110 X 120 110 X 120 120 120 120 120 120 120 120	ALNRKOGATOVANMI RCIKKLTDMOTSTMI RCIKKLTDMOTSTMI RCIKKLTDNOTSTMI RTIKKLTDNOTSTMI RTIKKLTDNOTSTMI RTIKKLNEKOI RTIKKLNEKOI DAMRADFRILRAMSEF ASLWKKAVCLPSILM	KATARS VVTCQR KATARS FRAVQR KRATR VVTCQR VTCQR TRMNP ITRLNP KLHCLL
Dm_AGO1_Q9V6V6 At_AGO1_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XGW1 Dm_PIWI_Q9VKM1 Dm_STING_076922 Hs_DICER_Q9UPY3 Dm_DICER_Q9VCU9	90 100 F - WYP LKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH KYNLQLKYPHLPCLQVGQEQ NHNVRLQYPNLPCILVKNG N-KKFIEFPHLPLVKVKSGA NGFTIQHTHLPCLQVGNQK KYNIIRDHNQPLLISKNR RYNIIRDLKQPLVMSRF RYNIIRDLKQPLVMSRF KYNLITNLNQPLLDVDHTSSR KYGLTIQNSQPLLDVDHTSR	NLLTPRHLNQKGKALPLS NFLTPRYVNRKGVALPTS	KH 	110 X 120 ILLPIELCSIEGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO AMLPIEFCFVVKGQ YAVPMEHLEVHEKP SYLPMEACKIVEGO VVLIPELCRVTGLN2 IMIIPELARATGMTI QILVPELCTVHPFP2	ALNRKDGATOVANNI RCIKKLTDMOTSTMI RCIKKLTDMOTSTMI RCIKKLTDNOTSTMI RXTAKLNSDGTANMI DRYKNRIDLVMODKFI DRYKRLNEKGI AEMRSNFQLMRAMSSY DAMRADFRTLRAMSEH ASLWRTAVCLPCILY	ATARS VTCQR ATARS FAVQR KRATR VTCQR TRMNP ITRLNP LHCLL LHCLL LINGLL
Dm_AG01_Q9V6V6 At_AG01_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XGW1 Dm_PIWI_Q9VKM1 Dm_STING_076922 Hs_DICER_Q9UPY3	90 100 R-NYPLKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH KYRLQLKYPHLPCLQVGQEQ KYNLQLKYPHLPCLQVGQEQ NHVRLQYPHLPCLUVGNG N-KKFIEFPHLPLVKVKSGA MYGFTIQHTHLPCLQVGNQK KYNIRIRDHNQPLLISKNR RYNIIIRDLKQPLNSRPT RYNLIRDKQPLLDVDHTSSRI	NLLTPRHLNQKGKALPLS NFLTPRYVNRKGVALPTS	KH 	110 X 120 ILLPIELCSIEGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO AMLPIEFCFVVKGQ YAVPMEHLEVHEKP SYLPMEACKIVEGO VVLIPELCRVTGLN2 IMIIPELARATGMTI QILVPELCTVHPFP2	ALNRKOGATOVANMI RCIKKLTDMOTSTMI RCIKKLTDMOTSTMI RCIKKLTDNOTSTMI RTIKKLTDNOTSTMI RTIKKLTDNOTSTMI RTIKKLNEKOI RTIKKLNEKOI DAMRADFRILRAMSEF ASLWKKAVCLPSILM	ATARS VTCQR ATARS FAVQR KRATR VTCQR TRMNP IRLNP LHCLL LINGLL
Dm_AGO1_Q9V6V6 At_AGO1_004379 Hs_IF2C1_Q9UL18 Sp_IF2C_074957 Ce_RDE-1_Q9XU82 At_Zwille_Q9XGW1 Dm_PIWI_Q9VKM1 Dm_STING_076922 Hs_DICER_Q9UPY3 Dm_DICER_Q9VCU9	90 100 F - WYP LKFPQLHCLNVGSSI KYRMKLRYPHLPCLQVGQEH KYNLQLKYPHLPCLQVGQEQ NHNVRLQYPNLPCILVKNG N-KKFIEFPHLPLVKVKSGA NGFTIQHTHLPCLQVGNQK KYNIIRDHNQPLLISKNR RYNIIRDLKQPLVMSRF RYNIIRDLKQPLVMSRF KYNLITNLNQPLLDVDHTSSR KYGLTIQNSQPLLDVDHTSR	NLLTPRHLNQKGKALPLS NFLTPRYVNRKGVALPTS	KH 	110 X 120 ILLPIELCSIEGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO TYLPIEVCNIVAGO AMLPIEFCFVVKGQ YAVPMEHLEVHEKP SYLPMEACKIVEGO VVLIPELCRVTGLN2 IMIIPELARATGMTI QILVPELCTVHPFP2	ALNRKDGATOVANNI RCIKKLTDMOTSTMI RCIKKLTDMOTSTMI RCIKKLTDNOTSTMI RXTAKLNSDGTANMI DRYKNRIDLVMODKFI DRYKRLNEKGI AEMRSNFQLMRAMSSY DAMRADFRTLRAMSEH ASLWRTAVCLPCILY	ATARS VTCQR ATARS FAVQR KRATR VTCQR TRMNP IRLNP LHCLL LINGLL

Accession numbers are indicated on the left. Abbreviations are: Dm *Drososphila melanogaster*, At *Arabidopsis thaliana*, Hs *Homo sapiens*, Sp *Schizosaccharomyces pombe*. Residue numbers, secondary structure, protein-RNA contacts (open/filled red squares for medium/strong chemical shift perturbation, see Fig. 2c,d), and solvent-protected amide protons (open/filled circles for medium/slow H/D exchange in NMR measurements) and mutations (blue "X") are shown on top. Partial, high or complete residue conservations are shown below the alignment with ".", ":" and "*" and residues are color-coded according to CLUSTALX (Jeanmougin, F., Thompson, J. D., Gouy, M., Higgins, D. G. & Gibson, T. J. Trends Biochem. Sci. 1998, 23, 403-5).

Note, that residues 120-143, following the last strand (7) are unstructured even in protein constructs extended N- and C-terminally, and a PAZ domain comprising residues 1-123 is structurally intact (data not shown).