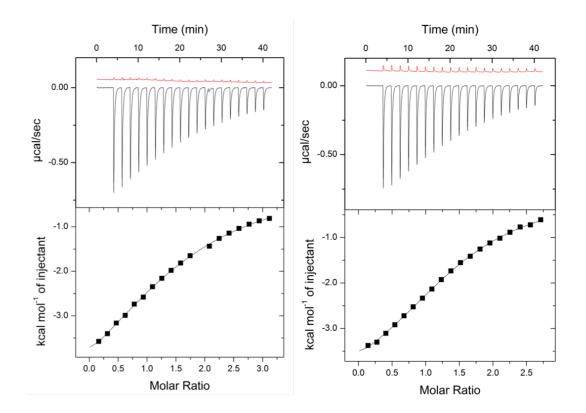
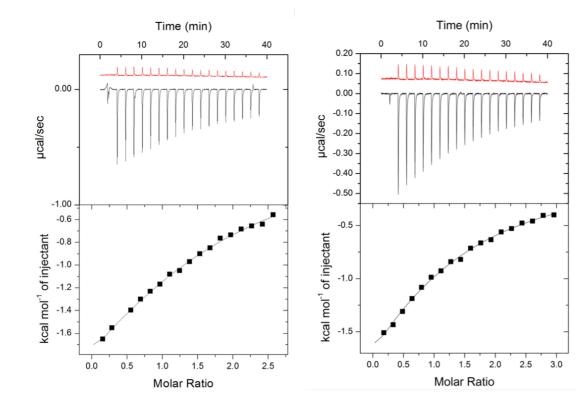
H3 4-mer (ARTK) vs BAZ2A PHD

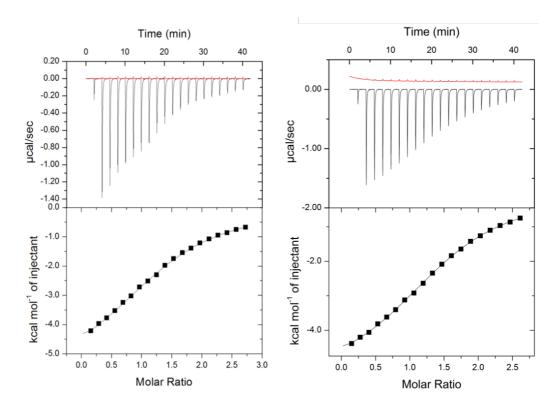
H3 4-mer (ARTA) vs BAZ2A PHD



H3 5-mer (ARTKQ) vs BAZ2A PHD

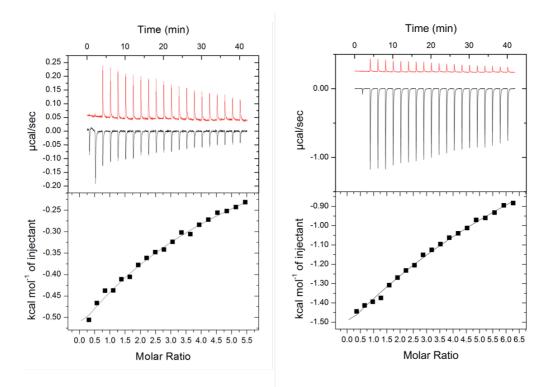


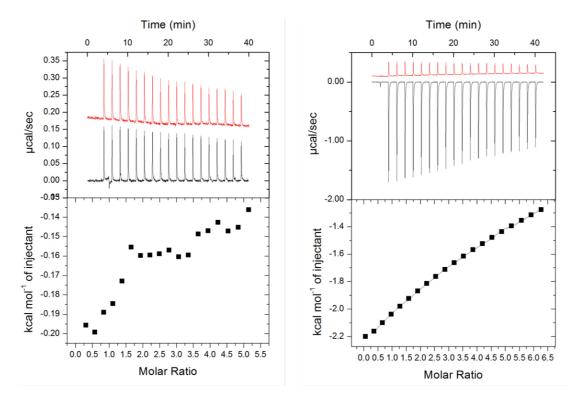






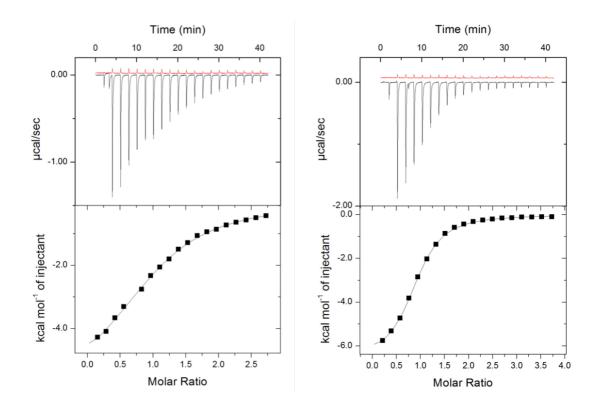
H3 10-mer (AATKQTARKS) vs BAZ2B PHD

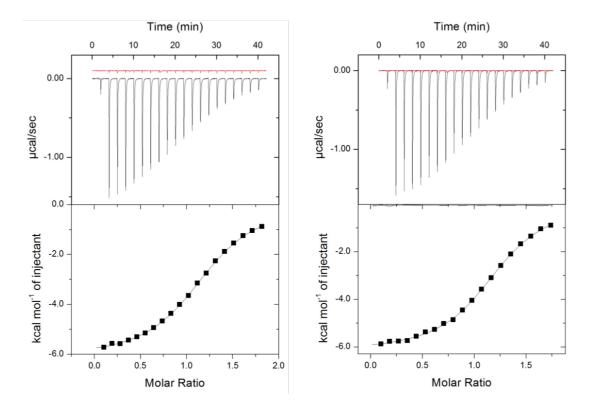




H3 10-mer (ARTAQTARKS) vs BAZ2A PHD

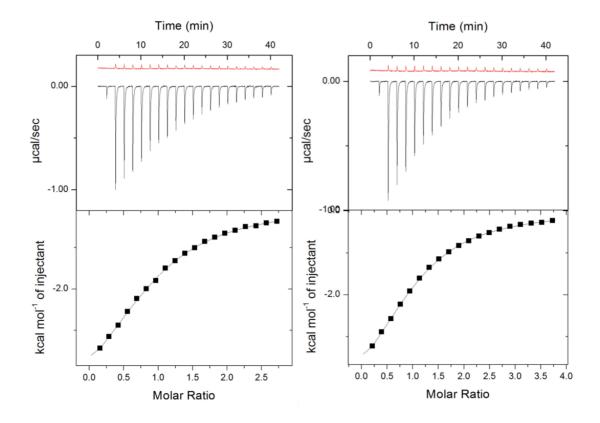
H3 10-mer (ARTAQTARKS) vs BAZ2B PHD

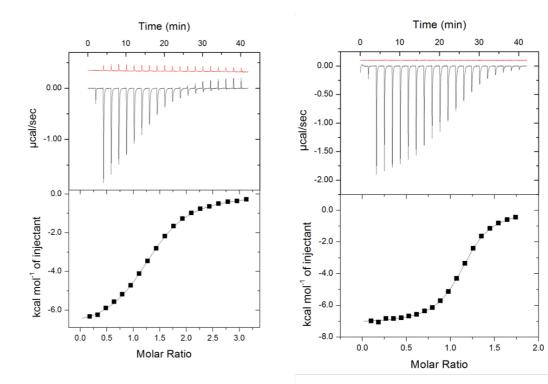




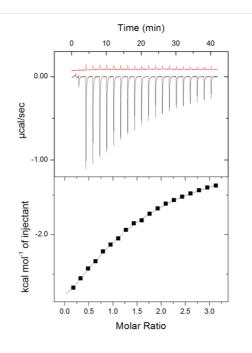
H3 10-mer (ARTKQAARKS) vs BAZ2A PHD

H3 10-mer (ARTKQAARKS) vs BAZ2B PHD





H3 10-mer (ARTGGTARKS) vs BAZ2A PHD



H3 10-mer (ARTGGTARKS) vs BAZ2B PHD

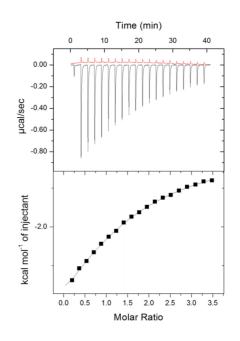
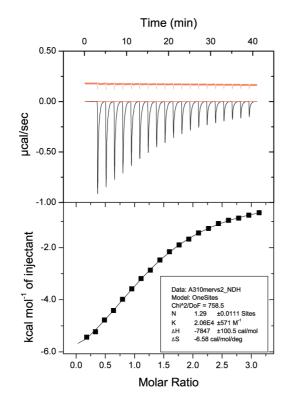
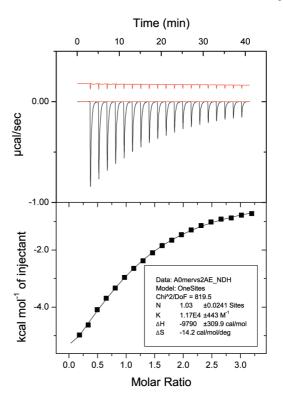


Figure S1. ITC binding curves of BAZ2A/B PHD fingers with different H3-derived peptides are shown in black and the relevant reference titrations (peptide into buffer) are shown in red in the upper panel. The integrated Δ H (kcal/mol) values are plotted versus the peptide/protein molar ratio and shown in the lower panel.



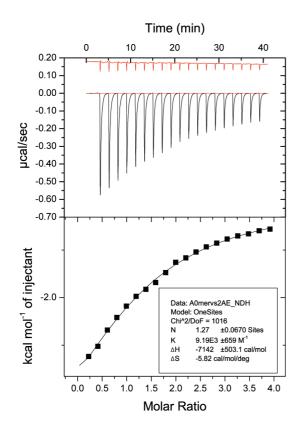
H3 10-mer vs BAZ2A PHD E1689Q

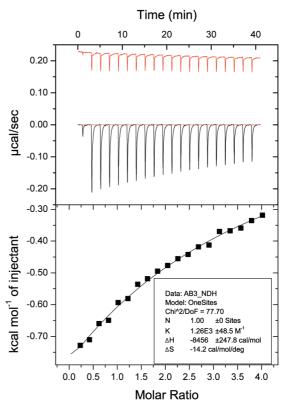


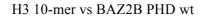




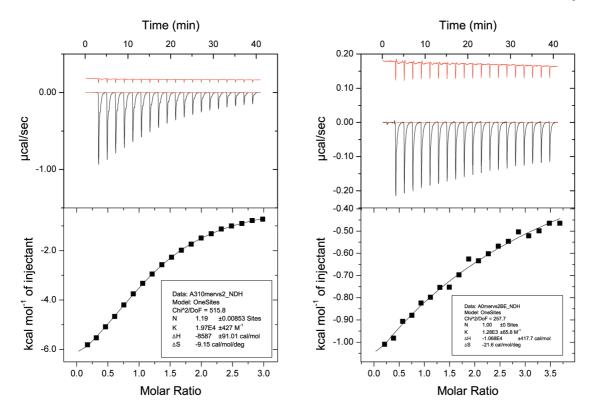
H3 10-mer vs BAZ2A PHD D1688N/E1689Q







H3 10-mer vs BAZ2B PHD E1689Q



H3 10-mer vs BAZ2B PHD E1689K

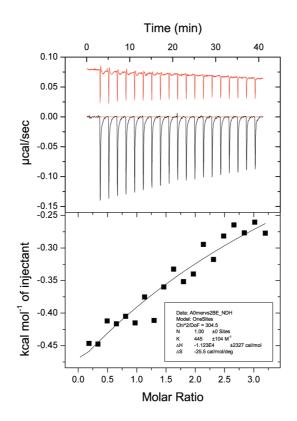


Figure S2. Representative ITC binding curves of wild-types and mutants BAZ2A/B PHD fingers with H3 10 mer peptide (ARTKQTARKS) are shown in black and the relevant reference titrations (peptide into buffer) are shown in red. In the lower panel, the integrated Δ H (kcal/mol) values plotted versus the peptide/protein molar ratio.

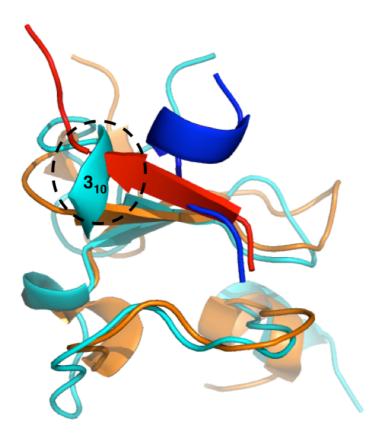


Figure S3. Structural superposition of the PHD fingers of BAZ2A (shown in cyan, PDB 5T8R) and ING2 (shown in orange, PDB: 2G6Q) in complex with an H3 N-terminal tail peptide (shown in blue for BAZ2A PHD and in red for ING2 PHD). A dotted black circle highlights the region where the H3 N-terminal peptide would clash with the 3₁₀ helix of BAZ2A PHD if the peptide assumed an extended conformation as the one observed in complex with ING2 PHD.

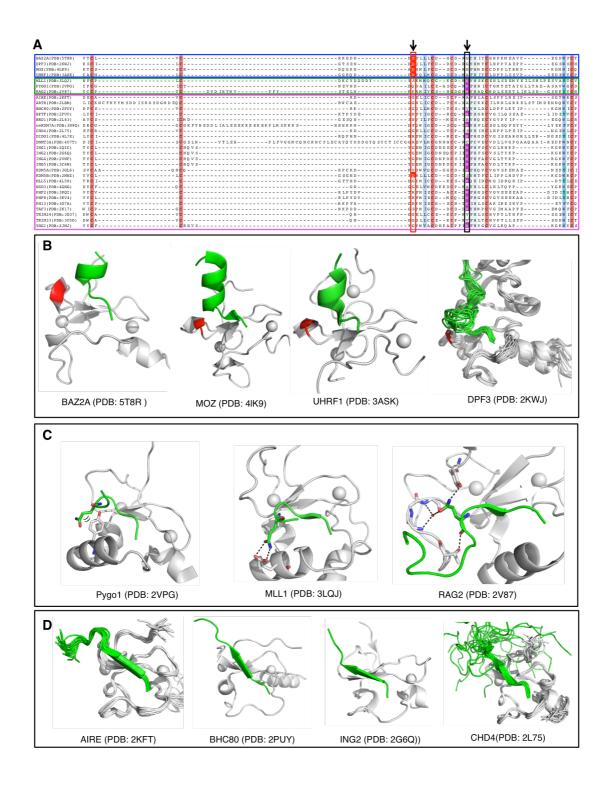


Figure S4. (A) Sequence alignment of all the PHD fingers whose structure was solved in complex with an H3 N-terminal tail peptide. Residues corresponding to E1689 of BAZ2A and residues corresponding to the absolutely conserved Trp of PHD fingers that recognize methylated-K4 are highlighted through the alignment with a red and a black box

respectively. PHD fingers in a blue box induce the H3 N-terminal peptide to adopt a helical folded-back conformation, in a green box induce H3 N-terminal peptide to adopt a bent conformation and in a magenta box bind H3 N-terminal peptide into an extended conformation **(B)** Structures of PHD fingers (shown in gray) that have an acidic residue (shown in red) in the position corresponding to E1689 of BAZ2A and that induce the H3 N-terminal peptide (shown in green) to adopt an helical folded-back conformation. **(C)** Structures of PHD fingers that induce the H3 N-terminal peptide to bend. In contrast to the recognition of helical folded-back H3 tail, the bent conformation of H3 bound to PHD appears to be stabilized by a different set of interactions. The interactions between PHD finger and H3 N-terminal peptide that stabilize the bent conformation are highlighted. Dotted lines represent hydrogen bonds and double brackets hydrophobic interactions. **(D)** Representative structures of PHD fingers that bind H3 N-terminal peptide in an extended conformation.

			T							
AIRE[1]	E C A V	C R DG G	E L	ICCDGC		LA	CLSPPLR-E	L P S G T	WR	CSSC
AIRE[2]	R C G V	CGDG	TDV	LRCTHC	A-AAF	WR	CHFPAGT - S	R P G T G	L R	CRSC
ASHIL	R C I	CGLYKDE	GLM	10CDKC	M – VWD	CD	CMGVNSD	V E H	Y L	CEOC
*ASH2L		NGRQL0								
ASXL1		C S L								
ASXL2		C R L								
ASXL3		C R L								
*BAZ1A\	R <mark>C</mark> K I	C R K K G D A								
*BAZ1B\	R <mark>C</mark> K – – – – – – – – – – – – V							V P D G E		
*BAZ2A	T <mark>C</mark> L V	C R K G D N D	- EFL	L L C D G C	D-RGC	H I Y	CHRPKME - A	V P E G D	W F	CTVC
*BAZ2B	Y CQI	CRKGDNE	ELL	L L C D - - G - - C	D-KGC	HT Y	CHRPKIT-T	I P D G D	W F	CPAC
BPTF[1]\	H <mark>C</mark> RV									
BPTF[2]\	YCI	СКТРҮ D- E S	- K F Y	I G C D - - R - - C	Q - NWY	G R -	CVG LQS - EA	ELIDE	Y V	CPQC
BRD1[1]\	VCCI	С М D G E C Q N S	NVI	LFCDMC	N-LAV	Q E	CYGVPY	P E G Q L T G G G T T	WL	CRHO
BRD1[2]\		C K Q K G								
	VCC	C N D G E C Q N - S		LFCDMC	N-LAV	QE			WL	CRRC
BRPF1[2]\ BRPF3[1]\		C L D D E C H N S	SGAC	IQCHKANC	Y - I AF	V I	CAQQAGL	YMKMEPVREIGANGIS	F-SVRKIAY	CDT
		СКОКС			N-LAV	QE			WL	CRCC
BRPF3[2]\ CHD3[1]\		C 0 0 G G	LUAA	TUCHKVNC		V I		PMRTEPMREISLNGTT	F-IVKKIAT	CEAR
CHD3[1]\ CHD3[2]\	Y CP	CKDGG			P - KAT				W	CPHC
CHD3[2]\ CHD4[1]\						MV			W C	CPKC
CHD4[1]\ CHD4[2]\		CKDGG			P - KAT				W	CPRC
CHD4[2]	Y C E V					1 V		AP EGK	W	СРИС
*CREBBP\		CFTEIQGE-NVTLGDDPSQPQTTISKDQFEKKKNDTLDF								
CXXC1	Y C	CRKPDIN	CEM			- C D		KAIRE	W V	CREC
DIDO1	YC	CROPHNN	REM	ICCD = R = -C	E = EWE	GD	CVGLSEA-RGRLLE	RNGED	Y 1	CPNC
*DPF1-1/11\		CLGGSKKTGCF								
*DPF1-1[2]	SCSL	CGT S E N DGA S WAG L T PC	DOL	L F C D D C	D-RGY	MY	C L S P P M A - E	P P E G S	WS	CHLO
*DPF1-2[2]\	SCSL	C G T S E N D	DOL	L F C D D C	D-RGY	MY	C L S P P M A - E	P P E G S	W S	CHLO
*DPF2[1]\	Y C D F	CLGDSKIN-KKTGOF	EEL	V S C S D C	G - R S G	P S	C L O F T P V - MM A A	V K T Y R	WO	CIEC
*DPF2[2]\	C C N I	CGT S E N D	- DO L	L F C D D C	D-RGY	MY	C L T P S M S - E	P P E G S	WS	CHLC
*DPF3[1]\	Y C D F	C L G G S NMN - K K S G R F	EEL	V S C A D C	G - R S G	РТ	C LQ FT L N - MT EA	V K T Y K	WQ	CIEC
*DPF3[2]\	S C I L							P P E G S		
*EP300\	F C E K	C F N E I Q G E – S V S L G D D P S Q P Q T T I N K E Q F S K R K N D T L D F	ELF	V E C T E C	G – R K M	Q I	CVLHHEI	I W P A G	F V	CDG
FBXL19		C G E A G K E D - T V E G E E E K F G								
ING1	Y <mark>C</mark> L	C NQ V S Y	- G E M	IGCDNDEC	P I E <mark>W</mark> F	F S – –	C VGLNH	КРКСК	W Y	СРКС
ING2	Y <mark>C</mark> L	CNQ V S Y	- G E M	IGCDNEQC	P I E <mark>W</mark> F	H F S – –	C V S L T Y	K P K G K	W Y	СРКС
ING3		C NQ V S Y								
NG4	Y <mark>C</mark> L		GEM	IGCDNPDC	SIEWF	F A – –	CVGLTT	K P R G K	W F	CPRO
NG5	Y C L	C HQ V S Y	GEM	IGCDNPDC	PIEWF	F A – –	CVDLTT	K P K G K	W F	CPRC
	ACVV	CRQMMVASG	- NQ L	V E C Q E C	H-NLY	R D – –	CHKPQVT - DK EAN	DPRLV	W Y	CARC
IHDM1D\	Y C V	CRQPY D- VN	RFM	I E C D I C	K – DWF	G S	CVGVEEH-HA	VDIDL	Y H	CPNC
KDM2A	TCSL	C G E V DQ N E E T Q D F I	EKKL	MECCIC	N-EIV	PG	LQMDGEG	LLNEELPNC	WE	CPKC
KDM2B\		G E A G K E D - T V E E E E G K F M L E E D G T	LML	MECSIC	N-EIII	P G	CLKIKES-EG	VVNDELPNC	WE	CPKC
KDM4A[1]\	MCFTSTGCSTDINLSTPY		SIL	VSCKKC	S-VRV	A S	CYGVPPA	K A S E D	WM	CSRC
KDM4A[2]\		C K K R R								
	MCFTSGGENTEPLPANSY	GDDGKKV9	SPL	ACGKC	C - LQV	A S	CYGIKPE	LVNEG	WT	CSRC
KDM4B[2]		C R K R M	GAC	LCCA K	S - TSF	V T	CARAGV		W-PYVVSIT	CAR
KDM4C[1]\	MERITSEENTETSPPNAF		SLL	1 5 CA K C	C - VKV	A 2	urur SH	EICDG	wL	CARC

			r			T					
*KDM5A[1]\ V	E 14	G R G N N E			60		T C		- V P K G D		DKCV
KDM5A[1]\ V	CF								-		
									- A E N E D		
	CLL		DRLLL	CDG	C D -	DSYH	T F C	LIPPLH-D	- VPKGD	WRC	PKCL
KDM5B[2]	C	СОКАРА							- Q G L R I		
	CPAVS								- A E K E D		
*KDM5C[1]\ V	C R M								– I P K G V – – – – – – – – – – – – – – – – – –		
KDM5C[2]\	C V								– S P R P N P T S – – – – – – – – S P		
	C QV								- I P R G I		
KDM5D[2]\									– SPKPSLTS––––––SP		
		С Е VWT									
KIAA1333[1]\ K	CCV	C K K N	GASIGO	CVAPR	CK-	RSYH	F P C	GLQREC	- 1 FQ FT GN	FASFC	WDHR
MLL2[1]\ R		C K C K E G K D - Y N A P	CASID			SGIH		SSLR S	wegn	wEC	DELIC
MLL2[2]\ R									- R K R A G		
MLL2[3]\ V		CRKPGND									
MLL2[4]\ M	CVV	C G S F G R G A E	GHLLA	cs o	C S -	OCYH	P Y 0	VNSKIT-KV	- M L L K G	WRC	VECI
MLL2[5]\ V	C E V	C G Q A S D P							- V P K G G		
*MLL2[6]\ T	CPI	C H A P Y V E E	DLLIQ	C R – – H	C E -	R WM H	AG(E S L F T E - D D V E	QAADEG	F DC	VSCQ
MLL2[7]\ K	C S L	Q R T	GATSS	CNRMR	– – <mark>C</mark> P –	NVYH	F A – – 🤇	A I R A K C	- M F F K D K	TMLC	РМНК
MLL3[1]\ R	C AF								- FQDFSHI		
MLL3[2]\ N		C D S P G – – D – – L – – – – – – – – – – – – – –	LDQFF	С Т – – Т	– – <mark>C</mark> G–	QHYH	GM – – (LDIAVT-P	– L K R A G – – – – – – – – – – – – – – – – – –	WQC	PECK
MLL3[3]\ V									- V P T N G		
MLL3[4]\ L		С									
MLL3[5]\ M	CVV CEA								– V L S K G – – – – – – – – – – – – – – – – – –		
MLL3[6]\ V *MLL3[7]\ S		C K A I D P									
MLL3[8]\ K	CV	Сткиткее	CATSC						- MEEKDK		PMHK
MLL4[1]\ V	CI	CASKGL	HELVE	CO = -V		DPEH	P F (- MTTROK	WCC	RRCK
MLL4[2]\ F	CHV	G R K G R - G S	KHLLE	C E R	C R -	HAYH	P A 0		TRKRRH	W	SACV
MLL4[3]\ Y	CPI	C T R C Y E D N D Y E	SKMMQ	CAQ	C D -	HWV H	AK (EGLSDE-DYEILS	G L P D S V L	YTC	GPCA
MLL4[4]\ R	C E L	C L K P	GATVG	CLSS	CL-	SNEH	FM 0	A R A S Y C	- I FODDK	KVFC	окнт
MLL5\ R		C G F T H D D									
interistry (C CV	C S D E R GWA – – E – – – – – – – – – – – – – – – –	NPLVY	CDGHG	– – <mark>C</mark> S –	VAVH	Q A (YGIVQ	- V P T G P	WFC	RKCE
	C YI	C D E Q G R E S	GACMT	CNKHG	– – <mark>C</mark> R –	QAFH	V T – – C	AQ F A G L	– L C E E E G N – – – – – – – – G A D	N VQY C	GYCK
		C S D E R GWA E	NPLVY	CDGHA	C S -	VVVH	QA(Y G I VQ	- V P T G P	WFC	RKCE
MLLT6[2]\ T	CYI	C E E Q G R E S	GACMT	CNRHG	CR -	QAFH	VT(AQMAGL	- LCEEEVLEVD	NVKYC	GYCK
MLL[1]\ V MLL[2]\ F		GROH O - AT	VEFVY			EPFF	KFC	LEENER-PLE	- DQ L E N	wcc	KKCK
MLL[2]\ F MLL[3]\ F		CDK CY DDDDY E	SKMMO		C K -		PEC			w	VNCT
MLL[4]\ R	CF	СОКР	CATYC	CLITS	CD-	SNVH	5 K C				OPHP
	CT	COEEYSEAP	NEMVI	CDK		OCYH	010	HTPHID-CSV		WLC	ROCV
MTF2[2]\ Y	CY	G G P G D - WY	LKMLO	ССК	СК -		EA 0	VOCLOK - P	- M L F G D R	FYTFIC	SVCS
*MYST3[1]\ I	C S F	C L G T K E O N - R E K	ELLS	CA D	CG-	NSGH	P S C	LKFSPE-LTV	R V K A L R	WOC	LECK
*MYST3[2]\ T	C S S	CR DQ G - K N A	DNMLF	C D S	C D -	RGFH	M E (CDPPLT-R	– M P K G M – – – – – – – – – – – – – – – – – –	WIC	QICR
*MYST4[1]\	C S F	C L G T K E S N – R E K – – – – – – – – – – – – – – – – – K P	EELLS	C A – – D	– – <mark>C</mark> G–	SSGH	PS(LKFCPE-LTT	N V K A L R	QC	IECK
*MYST4[2]\ T	C S A	C R V Q G - R N - A	DNM L F	C D S	– – <mark>C</mark> D –	RGFH	M E – – 🤇	C D P P L S - R	– M P K G M – – – – – – – – – – – – – – – – – –	WIC	QVCR
NSD1[1]\ V	C QN	CEKLG	- ELLL	CEA-Q	<mark>C</mark> C-	GAFH	L E (LGLTE	- M P R G K	FIC	NECR
	F V	C K Q S G		CLLPL	CG-	KFYH	E E (VQKYPP-TV	- MQ NK G	F R C	SLHI
NSD1[3]\ -	5T	C H A A N P A N – – – – – – – – – – – – – – – – – –	GREMRO	CV R	CP -	VAYH	ANDFO	LAAGSK	- I LASN		PNHF
NSD1[4]\ W NSD1[5]\ E	C FV	C S E G G					KEC				DWHO
ASD1[3]] E	• F		- 2 - 2 3	K			AD (- NFAGK	UV E L	rwng

PHF101 K K C <th></th>	
PHF11 IK CATUGCDLKN CN KN FF CAKUDDA VPQSDCVRC IV PHF12-101 SCD SC CKTUCCDLKN CN KN FF CAKUDDA VPQSDCVRC IV PHF12-101 SCD SCD SCD CKTUCDDH CKTUCDDH CKTUCDDH CKTUCDDH CKTUCDDH CKTUCDDH CKTUCDDH FF AKKSSN VPCD FF	
PHF12-12[1] S C - S C E E G - - C L L C D - H C P - AA F H Q - C N P I S - E E - - W PHF12-12[1] S C F - T C N S C C R - V - A P L L C D O - C L L F M D - S L F H G T - - W PHF12-12[1] S C - F C N K F F - A G P M H R N = C - C L L F M D - F M K F F - A G P M H R N = C - C C N P V L G O S A S I S I S S A S I S I S S A S I S I	ICDCCQ
PHF12-3/11 C F C NR S C R - V	KLLCQQHA
PHF13:10 SC SC PLCCOD H CP AAFLUV VQOPVAPI SLFHGT F PHF13:10 C F KKPFAAG PFMEGA C F<	
PHF131 T F MK PF A - G PPMIE A - G PPMIE A - T T K K S - N - V P EV - F PHF14-1121 E S F E DP R F ART CV C IS DAGM R A Y F VT AQK EG L S S AS ENST FP W PHF14-121 E S F E DP R F ART CV C IS DAGM R A Y F VT AQK EG L S S AS ENST FP W PHF14-121 E S F E DP R F ART CV C IS DAGM R A Y F VT AQK EG L MPR AKE S AS ENST FP W PHF131 D O V R X K H - D Q - K I H K L G L DP H T R MPR K TK S Y W MPR TA S AS ENST FP W W PHF131 V O V R S F GE D G M R K N N - V C K K H N - Q O V G I L M E X P K TA S AS ENST FP W PHF131 D O V R S P SE GE D G N UK N O - E N L C V Q A Y GO I K V R TA S AS ENST FN W W PHF131 D O V R S P SE GE D G N UK N O - K N L C V Q A Y GO I K V R F GO S - W W W PHF131 D O V R S P SE GE D G N UK N N O - N O S P GE GE D G N UK C O A Y GO I K V R F GO S - W W <td></td>	
IPHF14-1211 I C V C L G DN S E D - A DE L I Q C D - N - G C - T V H G C - C Y C V D C E S D S I M S S A S E N S T E P	
PHF14-12j1 S C. I C KMH - D - Q. HL LL LQ PLT C L LQ PLT MPRTXINSY W PHF14-2(1) C C T C T C LQ PLT	FCDACK
"PHF15[1] E C C VC PF SC C VC PF SC VC PF SC VC SC VC SC VC SC VC SC VC VC SC VC	FAYCKQHA
PHF151[1] V C D V C K S P E G E D G	QCSECD
PHF15[2]) S C S L K E C	ICQECD
PHF16[1] I D V R S P D S E E - G N MDM Y E D - K - E N - V C Y G L K	– – – – L <mark>C</mark> R T C A
PHF16[2] V C N L C K L K T C A C L Q C S I K S C I T A F YT C A F E H C L E M YT L D E G D E V K F PHF17[1] V C D V C Q S P D G D - G N E M Y F C D - K C N - I (C V HQ A - C Y G I L K) V P G S W PHF17[2] V C S L C N E K N E M Y F C D - K C N - I (C V HQ A - C Y G I L K) V P G S S W PHF17[2] V C S L C N K K N E I L I C G - K C N - I (C V HQ A - C Y G I L K) P M N T L A - E ND E V K F PHF19[2] V C S L C N K K N E I L I C G - K C N - I (C V HQ A - C Y C I L K) E M N T L A - E ND E V K F PHF19[2] Y C S V C G C G C = E W N L K M L Q C R - C G - C L C Y R C R P - D - M M F C D R - N - F Y E F PHF12[1] L C C V C R S E T V V P - G N R L Y S C E - K - C R + A A HQ D - C HP A P A P E G E G C T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M P A P A P - C E G E G T S - W - M C A C K R G A - M P A P A P - C E G C G C T C C Q G R S V C M G L L E E - N - V P K V - Y P F E - P + F P P F P P P P P P P P P P P P P P	
PHF17121) V C D V C Q S P D G E D G NE MY F C D K N I C Y C A C Y G L K V C G L K V P E G S V M I L A END E V K F PHF17121) Y C S L C N E K N E I L I C G K K N C A F D R G L END E V K F P M E I L I C G K V N C A F D R G L END E V K F P M E I L I C G K V N C A F D R G L END E V K F P M E I L I C G K V N C A F D R G L END E V K F P M E I L I C G K V N C A F D R G L END E V K F P M E I L I C G K V N C G C P G E END E V V P C C C C C C C C C C C C C C C C C C C	
PHF17[2] V C S L C N E K F G A S I Q C S V K N C A T A C H V T C A F D A C L EMK T I L A END E V K F PHF19[2] V C S I C L K T S G P N EI L I C G - K - C C - I G Y H Q - C H I P I A G - S A D Q L L T P	KSYCLKHS
PHF19[1] K C N I C L G K T S G P - L	
PHF19[2]) Y C Y C G G P G - E - WY L R M LQ C Y - R C R - Q W F H E A C T Q C L N E - P MM F G D R	
PHFI[1] L C V C S C V C S C C V C S C C V C S C </td <td> FCSVCN</td>	FCSVCN
PHF1[2] Y C Y C G G F E A	VCROCV
PHF20L11 R C I C EMD E E N G FM 1Q C E E C L Q Q H S V C M G L L E E S I P EQ Y *PHF2201 R C I C EVQ E E N P P F G S V R K S G Y Y	ECVCR
PHF21A1 F C S	
PHF2181 H C A A C K R G A	TCYVCQ
PHF231 T C	
PHF2\ Y C V C R L P Y - D - V T R F M I E C D - A - C K - D W F H G S - C V G V E E E E A - P D I D I Y - P H F M I S C G - R - C D - D W F H G D - C V G V E E - E A P D I D I Y - P H F M I S C G - R - C D - D W F H G D - C V G V E E - E A P I D I D Y - P H F M I C A L H D K A Q I E K P S Q G Y	
PHF31 Q C G F C K K P H - G - N	– – – – Y <mark>C</mark> Q K C K
PHF6[1] MCS LCHCP CATIGCDVKT CH-RTYHYH CALHDKA QIREKPSQC IY PHF6[2] KCT LCSQP CATIGCDVKT CH-RTYHYH CALHDKA QIREKPSQC IY PHF6[2] KCT LCSQP CATIGCDVKT CH-RTYHYH CALHDKA QIREKPSQC IY PHF6[2] KCT LCSQP CATIGCDVKT CH-RTYHYH CALHDKA VIREKPSQC IY PHF7[1] ICF VCKKK GAAINCQKDQ CL-RNFHLP CGQQDKA KY IENMSRG IY PHF7[2] ICF VCKKK GAAINCQKDQ CL-RNFHLP CGQVDKA KY IENMSRG IY PHF7[2] ICF VCKKK GAAINCQKDQ CL-RNFHLP CGVCVEE SQLRS NSKK W PHF7[2] ICTCRTSON CRSSD-R ECRWCLILCA CQDWCKA ADIDL Y Y PHF7[2] ICCCCCCCQRSD REGRWCLILCA CQDWCKA ICCCVCVEE NSKK W Y Y Y Y Y Y Y Y Y Y Y Y Y Y Y	HCPNCE
PH6[2] K C T L C S Q P C A T I G C E I KA C V - K T Y HY H C G V Q D K A K Y I E NM S R G I Y PH6[2] K C T C A T I G C E I KA C V - K T Y HY H C G V Q D K A K Y I E NM S R G Y PH6[2] I C F V C K K K G A I N C Q K D Q C L = N F H L P C G Q E R G C L S Q F F G E Y PH6[2] I C F V C K K K C A I N C Q K D Q C L = N F H L P C G S L R S N K K PH7[2] I C L Y E Q G R D - S F E D C G R W C L I L C A - T C G S H G T H R D C S S L R S N K K PH7[2] I C L Y E Q G R D - S F E D C G R W C L I L C A - T C G S H G T H R D C S S L R S N K K PH7[3] Y C C L C R L P Y D V T R F M I E C D - M C Q - M F H G S C V G V E E - K A A D I D L Y PH7[3] Y C G L C R D - R D - M - C A G Y H M C L G G R S D - R R M I E C D - G C - G G A G Y H M C L C D A G Y H M C L C D - G C A G Y H M C L L X E A S A V W PYGO1 P C G I C T N E V N D D Q D A I L C E A - S Q Q - K W F H R I C T G M T E - A Y C L L T A E A S A V	
PHF7[1] I C F	
PHF7[2] ICLYEQGRD-SFED EGRWCLILCA-T-CGSHGTHRD-CSSLRS NSKK PHF7[2] RFMIECD RGWCLILCA-T-CGSHGTHRD-CSSLRS NSKK PHF7[2] RFMIECD NSKK NSKK PHF7[2] RFMIECD NSKK NSKK PHF7[2] RFMIECD NSKK NSKK PHF7[2] RC NSKK NSKK PHF7[2] PGD1 RC NSKK PYG01 PC C CAGYMME CLOPPLQ PYG021 PC GC ACRSEVNDD QDAILCEA-S CQ-KW FHRI- CTGMTES-AY PYG021 PC GC ACRSEVNDD QDAILCEA-S CQ-KW FHRE CTGMTES-AY GLLTTEASAV PKG2[2] PC GC ACRSEVNDD QDAILCEA-S CQ-KW FHRE CTGMTES-AY GLLTTEASAV PKG2[2] PCG ACRSEVNDD QDAILCEA-S CQ-KW FHRE CTGMTES-AY GLLTTEASAV PKG02[PCG ACRSEVNDD QDAILCEA-S CQ-KW FHRE CTGMTES-AY GLLTTEASAV PKG02[PCG ACRSEVNDD QDAILCEA-S CQ-KW FHRE CTGMTES-AY	
PHF8\ Y C L C R L P Y - D - V T R FM I E C D - M - C Q - D W FH G S - C V G V E E - KA A D I D L Y	
**PHRF1\ FCE FCE CLDPPLQ-E VVDE W PYG01\ PCG ICTNEVNDD QDAILCEA-S CQ-KWFHRI-CTGMTET-AY GLLTAEASAV W PYG02\ PCG ACRSEVNDD QDAILCEA-S CQ-KWFHRE CTGMTES-AY GLLTEASAV W PYG02\ PCG ACRSEVNDD QDAILCEA-S CQ-KWFHRE CTGMTES-AY GLLTEASAV W RAG2\ YST SCOEA ELNKPAMIYCS GCHGCHKG GLHTHA-LSAGSNK Y- GATLGCCHKG CLHTHYNYC ASAGSC ILEEN F- CASAGC ILEEN	HCPNCE
<i>PYGO2</i> P C G	FCPECA
RAG2 Y ST	GCDTCM
RA(1) MCS	ACDLCL
	– – S L K <mark>C</mark> P K H K
*RSF1 PCKKCGLPN-H-P	FCPPCQ
SP110 E C E V C C Q G G	SCIFCR
SP140L EC	
574701 EE	
7/7/5/19 - C C L P O E - E - T	
TCF201 KCS	
7 <i>RIM2</i> 4) WCA	
<i>TRIM28</i> [1] HCGVCRERLRPE-REAANSSGDGG-AAGDGTGPAKSRDG	
<i>TRIM28</i> (2) I CRVCQKPGVPGEE	
<i>TRIM33[2]</i> WCA	ICTFCR

			↓		↓		
TRIM66[1]\	N <mark>C</mark> S E C	C K E K R	- ĂA H I	I L <mark>C</mark> T Y	C N – R	LCSS	S S – – <mark>C</mark> T E E H R H S P V P G G P F F P R A Q K G S P G V N G G P G D – – – – – – F – – – – T L Y <mark>C</mark> P L H T
TRIM66[2]	F <mark>C</mark> A V (C L N G G	E L L	L C <mark>C</mark> D R	СР-КV	FHLS	L S – – <mark>C</mark> H V P A L L – S – – – – – – – – F P G G E – – – – – – – – – – – – – – – – –
*UBR7	Y <mark>C</mark> I (C K R P Y – P D – P E D E – – – – – – – – – – – – – – – – I I	DEM I	I Q C V V	C E – DW	FHGR	GR – – <mark>H</mark> L G A I P – – – – – – – – – – – P E S G D – – – – – – – – – – – – – – – – F – – – Q EMV <mark>C</mark> QACM
*UHRF1\ A	A <mark>C</mark> H L (GGRQDP	- DKQL	LMCDE	CD-MA	FHIY	I Y <mark>C</mark> L D P P L S - S V P S E D E W
UHRF2\	S C R V C	C G G K H – – E – – P – – – – – – – – – – – – – –					I Y <mark>C</mark> L N P P L D - K V P E E E Y
*WHSC1L1[1]\ \	V <mark>C</mark> QI (E	- DSLI	IPCEG-E	СС-КН	FHLE	L E – – <mark>C</mark> L G L A S – – – – – – – – – – L P D S K – – – – – – – – – – – – – – F – – – –
WHSC1L1[2]\ F	P C F S (EA <mark>C</mark> VRK FPT-AIFESKGFFFF
WHSC1L1[3]\ -	– C S – – – – – – – – – – – A C	C S M E K D I H					S G D A <mark>C</mark> I A A G S M L V S S Y I L I <mark>C</mark> S N H S
WHSC1L1[4]\ -	- <u>-</u> K (P E – – <mark>C</mark> L S I – – – – E – – – – – – – – MP EGC – – – – – – – – – – – – – – – – – – W– – – – – – – N <mark>C</mark> NDCK
	Y <mark>C</mark> F Q (L L – – <mark>C</mark> L N L T Q – – – – – – – – – – – P P Y G K – – – – – – – – – – – – – – W – – – –
		ЕКР G					L A <mark>C</mark> L G L S R R P E G R F
WHSC1[2]\	· · ·	<mark>C</mark> K E S K					E A <mark>C</mark> V K K Y P L - T V F E S R G F
WHSC1[3]\							S G D A <mark>C</mark> L A A G C S V I A S N S I I <mark>C</mark> T A H F
WHSC1[4]\ V		S K G G			- · · · · · ·		P D <mark>C</mark> L N I E MP DG S W
	ECFR(L S <mark>C</mark> L G L G K R P F G K W E <mark>C</mark> P W H H
ZMYND11		CHLPG					SK <mark>C</mark> L S D E F R - L R D S S S P W
ZMYND8	Y <mark>C</mark> W V (HREG	Q V L	C C E L	CP - RV	Υ <mark>Η</mark> ΑΚ	A K – – <mark>C</mark> L R – – L T – S – – – – – – – E P E G D – – – – – – – – – – – – W – – – – – F <mark>C</mark> P E C E

Figure S5. Sequence alignment of human PHD fingers (Structural Genomics Consortium database, at http:// www.thesgc.or). The column corresponding to E1689 of BAZ2A is highlighted through the alignment with a red box and a black arrow, and Asp or Glu residues in this column are colored in red. The column corresponding to the absolutely conserved Trp in PHD fingers that recognize methylated-K4 is highlighted through the alignment with a magenta box and a black arrow, and Trp residues in this column are colored in magenta. Sequences that have an Asp or a Glu in the position corresponding to E1689 of BAZ2A are marked with an asterisk (*).

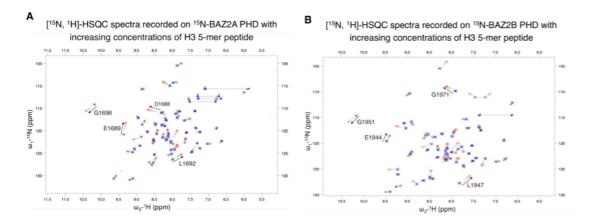
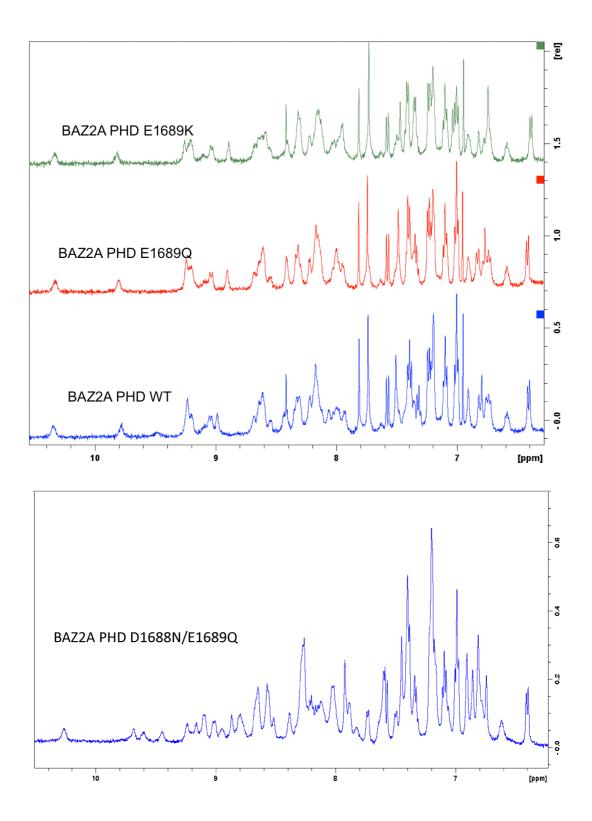


Figure S6. Characterization of the interaction between the H3 N-terminal tail and BAZ2A PHD and BAZ2B PHD in solution by NMR. (A and B) Overlay of [¹⁵N, ¹H]-HSQC spectra recorded on ¹⁵N-BAZ2A PHD **(A)** and on ¹⁵N-BAZ2B PHD **(B)** with increasing concentrations of H3 5-mer peptide (ARTKQ). Spectra were recorded at the following protein:peptide molar ratios: 1:0 (blue spectra), 1:2 (cyan), 1:4 (orange) and 1:8 (red). For a set of peaks the direction of the shifts are indicated with black arrows. All the backbone amide protons of BAZ2A PHD and BAZ2B PHD were assigned except for the first serine residue of BAZ2A PHD (BMRB deposition numbers: 26754 and 25988, for BAZ2A PHD and BAZ2B PHD, respectively).



S18

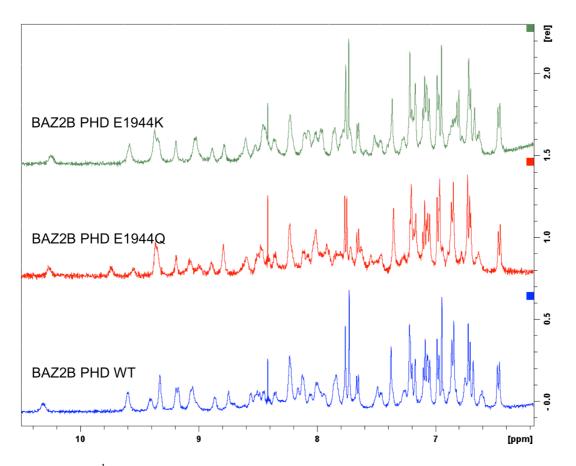


Figure S7. ¹H 1D NMR spectra were recorded on WT and mutants BAZ2A and BAZ2B PHD fingers and all the samples show a significant dispersion of the signals from the backbone NH groups suggesting that the proteins are folded. The spectra were recorded on samples at a concentration of 60 μ M in a buffer containing 10 mM Na₂HPO₄ pH 6.0, 50 mM NaCl, 1 mM DTT and 0.02% w/v NaN₃ and 10% v/v D₂O.

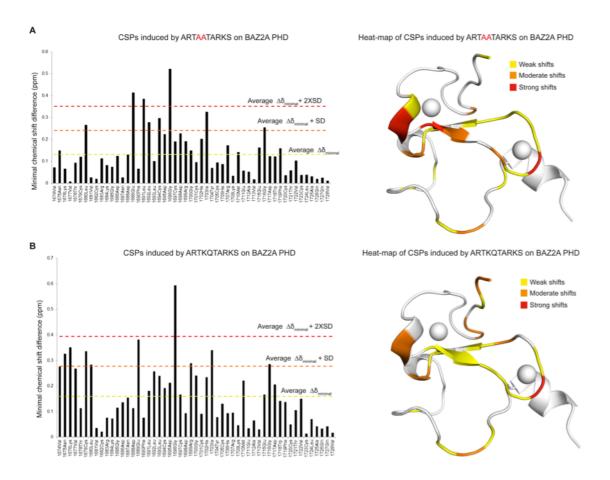


Figure S8. CSPs induced by H3 10-mer wild-type (ARTKQTARKS) and double-Ala mutant (ARTAATARKS) peptides on BAZ2A PHD. Consistent with a tighter binding affinity, most the shifts induced by H3 10-mer double-Ala mutant peptide (ARTAATRAKS) are in the slow exchange regime on the NMR timescale and peaks shifts are difficult to follow. To allow unbiased analysis of the double-Ala mutant peptide CSP data we used the "minimal-shift approach" (material and methods). The minimal shifts found were plotted against BAZ2A PHD sequences, clustered into weak, moderate and strong shifts (as described in material and method) and used to generate a heat-map representative of the peptide binding site (A). To allow direct comparison the same approached was used to analyze the CSPs induced by H3 10mer wild-type (ARTKQTARKS) (B).

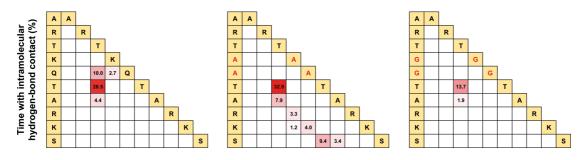


Figure S9. Intramolecular hydrogen-bond contacts within the 10-mer wild-type (ARTKQTARKS), double-Ala (ARTAATARKS) and double-Gly (ARTGGTARKS) mutant peptides in complex with BAZ2A PHD occurring during the last 60 ns of MD simulations, reported as the median percentage of time with contact out of 4 replicas. Median intramolecular hydrogen bond times below 1% have been omitted for clarity. In 10-merAA, a clear "i to i+4" pattern characteristic of α -helices is found.

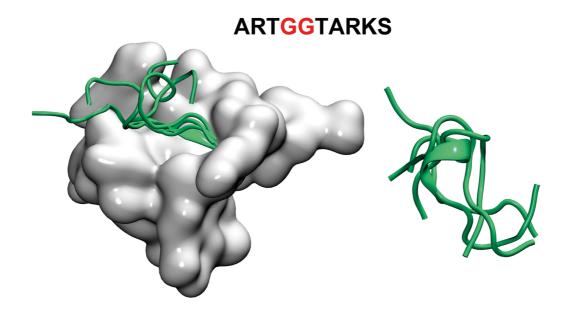
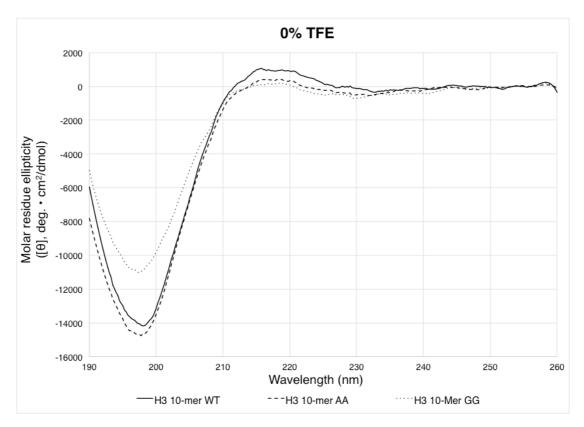
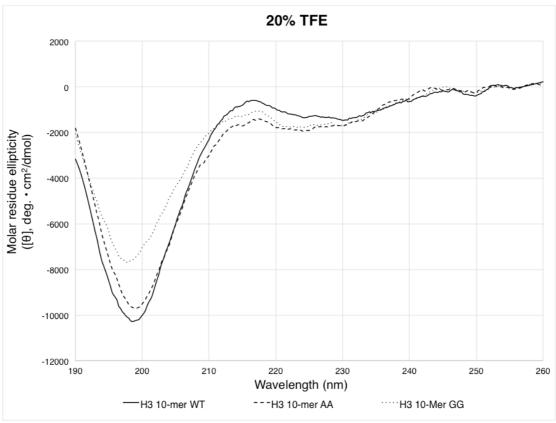
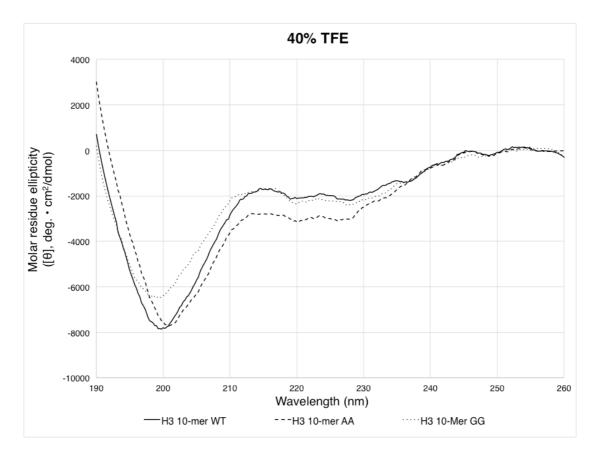
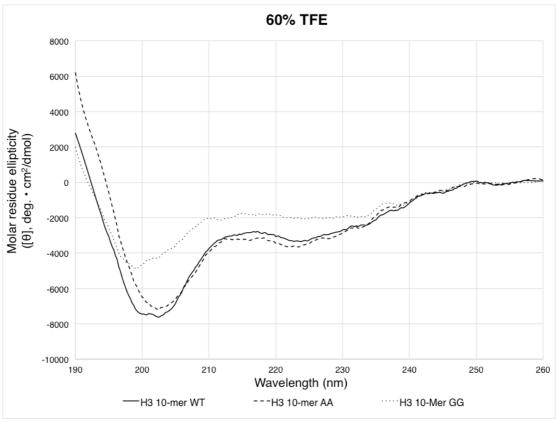


Figure S10. Superposed cartoon representation of the last frame of four MD replicas of ARTGGTARKS in complex with BAZ2A PHD (left) and in aqueous solution (right).









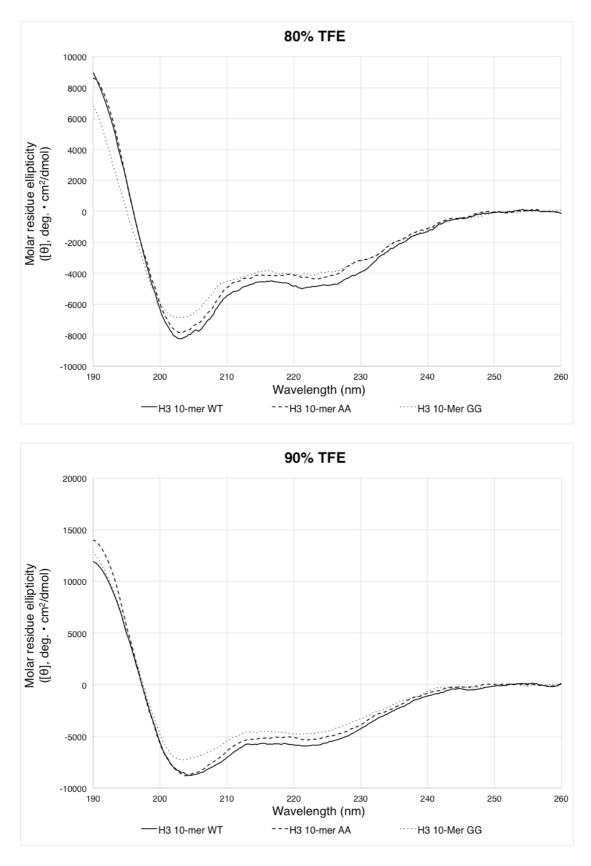


Figure S11. CD spectra recorded on samples of the H3 10-mer WT (ARTKQTARKS), H3 10-mer AA (ARTAATARKS) and H3 10-mer GG (ARTGGTARKS) peptides at different TFE concentrations (v/v).

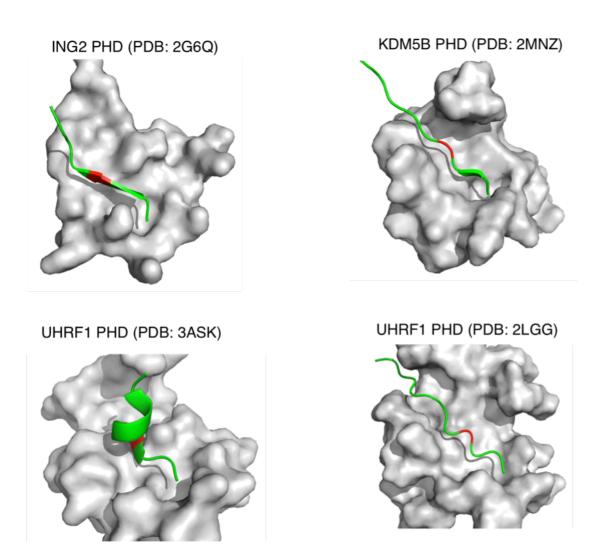
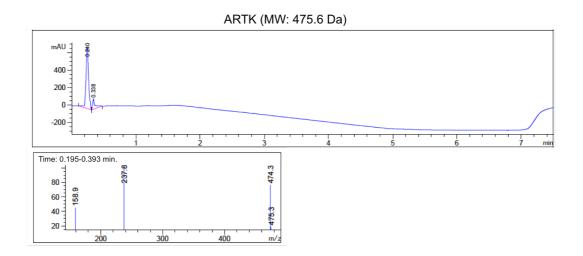
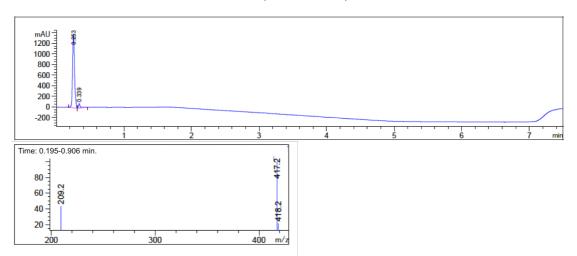


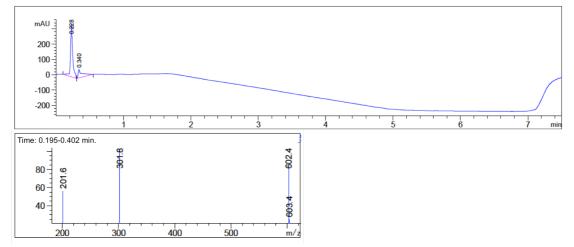
Figure S12. Structures of the PHD fingers of ING2, KDM5B and UHRF1 (shown in grey and surface representation) in complex with H3 N-terminal peptide (shown in green and cartoon representation). The K4 of H3 peptide is colored in red.

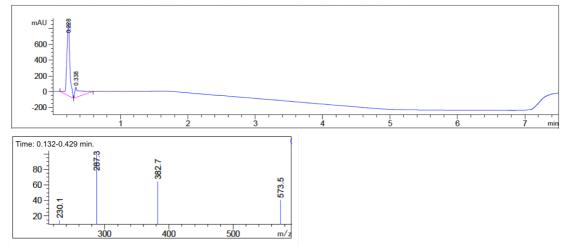


ARTA (MW: 417.5 Da)

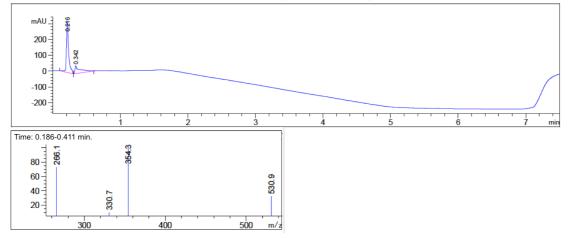


ARTKQ (MW: 602.7 Da)

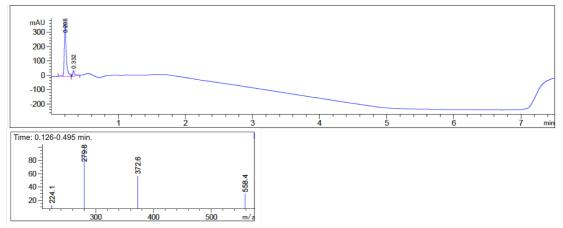




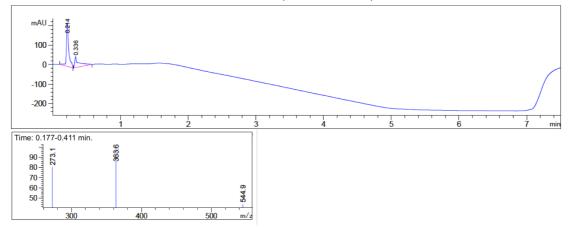
AATKQTARKS (MW: 1061.2 Da)



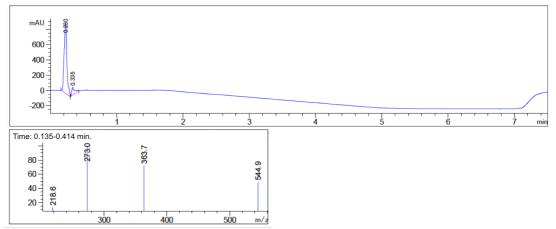
ARAKQTARKS (MW: 1116.3 Da)



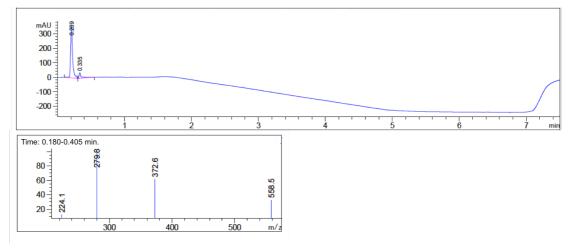
S28

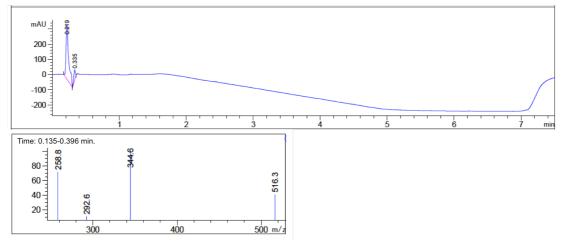


ARTKATARKS (MW: 1089.2 Da)



ARTKQAARKS (MW: 1116.2 Da)





ARTGGTARKS (MW: 1004.1 Da)

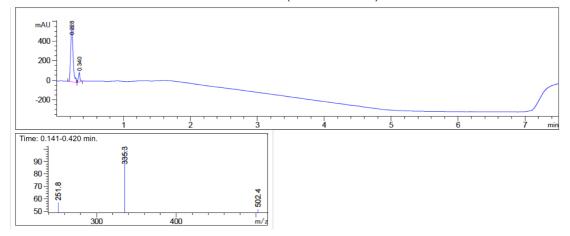


Figure S13. Liquid chromatography mass spectrometry (LCMS) analysis of H3 N-terminal peptides. For each peptide is reported the expected molecular weight (MW), the chromatogram monitoring absorption at 210 nm (upper panel) and the MS spectrum (lower panel).

H3 10-mer WT												
TFE % (v/v)	Result	Helix1	Helix2	Strand1	Strand2	Turns	Unordered	Total				
0%	1	0	0.103	0.194	0.111	0.223	0.368	0.999				
	2	0	0.061	0.226	0.128	0.214	0.372	1.001				
20%	1	0	0.104	0.189	0.116	0.245	0.346	1				
	2	0.004	0.067	0.236	0.128	0.22	0.344	0.999				
40%	1	0	0.095	0.209	0.118	0.239	0.338	0.999				
	2	0.007	0.068	0.247	0.128	0.218	0.332	1				
60%	1	0.018	0.109	0.196	0.115	0.238	0.323	0.999				
	2	0.026	0.085	0.231	0.123	0.222	0.314	1.001				
80%	1	0.068	0.109	0.177	0.106	0.224	0.315	0.999				
	2	0.058	0.094	0.189	0.111	0.231	0.317	1				
90%	1	0.093	0.117	0.161	0.102	0.222	0.306	1.001				
	2	0.08	0.106	0.169	0.105	0.229	0.312	1.001				

Table S1. Estimation of the secondary structure content of the H3 10-mer WT (ARTKQTARKS) peptide from deconvolution of CD spectra acquired at different TFE concentrations. Helix1 is the content of regular α -helix; Helix2 of distorted α -helix; Strand1 of regular β -sheet and Strand2 of distorted β -sheet. Result 1 reports the secondary structure content found using the closest matching solution during deconvolution and Result 2 the average of all matching solutions.

	H3 10-mer AA											
TFE % (V/V)	Result	Helix1	Helix2	Strand1	Strand2	Turns	Unordered	Total				
0%	1	0	0.103	0.184	0.114	0.231	0.368	1				
	2	0.002	0.062	0.202	0.123	0.221	0.39	1				
20%	1	0	0.091	0.199	0.118	0.239	0.353	1				
	2	0.005	0.064	0.229	0.125	0.221	0.356	1				
40%	1	0.014	0.095	0.208	0.112	0.23	0.341	1				
	2	0.02	0.074	0.233	0.12	0.219	0.335	1.001				
60%	1	0.034	0.098	0.199	0.113	0.228	0.327	0.999				
	2	0.035	0.085	0.237	0.122	0.214	0.308	1.001				
80%	1	0.059	0.104	0.188	0.111	0.227	0.311	1				
	2	0.048	0.091	0.204	0.118	0.231	0.309	1.001				
90%	1	0.094	0.106	0.175	0.104	0.215	0.306	1				
	2	0.069	0.097	0.182	0.112	0.224	0.314	0.998				

Table S2. Estimation of the secondary structure content of the H3 10-mer AA (ARTAATARKS) peptide from deconvolution of CD spectra acquired at different TFE concentrations. Helix1 is the content of regular α -helix; Helix2 of distorted α -helix; Strand1 of regular β -sheet and Strand2 of distorted β -sheet. Result 1 reports the secondary structure content found using the closest matching solution during deconvolution and Result 2 the average of all matching solutions.

	H3 10-mer GG												
TFE % (V/V)	Result	Helix1	Helix2	Strand1	Strand2	Turns	Unordered	Total					
0%	1	0	0.092	0.204	0.119	0.227	0.357	0.999					
	2	0.001	0.057	0.234	0.131	0.216	0.36	0.999					
20%	1	0	0.089	0.208	0.121	0.235	0.347	1					
	2	0.005	0.059	0.24	0.13	0.219	0.348	1.001					
40%	1	0	0.093	0.215	0.119	0.237	0.337	1.001					
	2	0.006	0.064	0.245	0.127	0.218	0.34	1					
60%	1	0.004	0.081	0.223	0.126	0.236	0.329	0.999					
	2	0.01	0.061	0.264	0.136	0.217	0.312	1					
80%	1	0.043	0.094	0.199	0.114	0.227	0.322	0.999					
	2	0.041	0.083	0.224	0.12	0.222	0.31	1					
90%	1	0.074	0.093	0.192	0.11	0.216	0.316	1.001					
	2	0.051	0.083	0.205	0.119	0.226	0.317	1.001					

Table S3. Estimation of the secondary structure content of the H3 10-mer GG (ARTGGTARKS) peptide from deconvolution of CD spectra acquired at different TFE concentrations. Helix1 is the content of regular α -helix; Helix2 of distorted α -helix; Strand1 of regular β -sheet and Strand2 of distorted β -sheet. Result 1 reports the secondary structure content found using the closest matching solution during deconvolution and Result 2 the average of all matching solutions.

Primer Name	Sequence (from 5' to 3')
F_BAZ2A_PHD_E1689Q	CGCAAAGGCGATAATGATCAGTTTCTGCTGCTGTGTGAT
R_BAZ2A_PHD_E1689Q	ATCACAGCAGCAGAAACTGATCATTATCGCCTTTGCG
F_BAZ2A_PHD_E1689K	CGCAAAGGCGATAATGATAAATTTCTGCTGCTGTGTGAT
R_BAZ2A_PHD_E1689K	ATCACAGCAGCAGAAAATTTATCATTATCGCCTTTGCG
F_BAZ2B_PHD_E1944Q	CGCAAAGGCGATAATCAGGAACTGCTGCTGCTGTGC
R_BAZ2B_PHD_E1944Q	GCACAGCAGCAGCAGTTCTGCATTATCGCCTTTGCG
F_BAZ2B_PHD_E1944K	CGCAAAGGCGATAATAAAGAACTGCTGCTGCTGCG
R_BAZ2B_PHD_E1944K	GCACAGCAGCAGCAGTTCTTTATTATCGCCTTTGCG
F_BAZ2A_PHD_D1688N/E1689Q	CGCAAAGGCGATAATAATCAGTTTCTGCTGCTGTGTGAT
R_BAZ2A_PHD_D1688N/E1689Q	ATCACAGCAGCAGAAACTGATTATTATCGCCTTTGCG

Supplementary Table S4. Primers used to perform site directed mutagenesis.

System	Nr. replica	Duration (ns)	Temperature (mean ± 1*σ, K)	Total energy (mean ± 1*σ, kcal/mol)	RMSD _{BAZ2A} from crystal (mean ± 1*σ, Å)
	1	80	299.5 ± 1.0	-54786 ± 151	1.4 ± 0.2
BAZ2A	2	80	299.5 ± 1.0 299.5 ± 1.0	-54780 ± 131 -54788 ± 245	1.4 ± 0.2 1.4 ± 0.3
10-mer	3	80	299.5 ± 1.0 299.5 ± 1.0	-54789 ± 151	1.4 ± 0.3 1.3 ± 0.2
10-11101	4	80	299.5 ± 1.0 299.5 ± 1.0	-54779 ± 151	1.9 ± 0.2 1.9 ± 0.5
	1	80	299.5 ± 1.0 299.5 ± 1.0	-54523 ± 150	1.9 ± 0.3 1.4 ± 0.2
BAZ2A	2	80	299.5 ± 1.0 299.5 ± 1.0	-54523 ± 150 -54521 ± 150	1.4 ± 0.2 1.4 ± 0.3
10-mer	3	80	299.5 ± 1.0 299.5 ± 1.0	-54525 ± 151	1.4 ± 0.3 1.4 ± 0.2
AA	4	80	299.5 ± 1.0 299.5 ± 1.0	-54523 ± 151 -54523 ± 150	1.4 ± 0.2 1.4 ± 0.2
	1	80	299.5 ± 1.0 299.5 ± 1.0	-54544 ± 150	1.4 ± 0.2 1.5 ± 0.3
BAZ2A	2	80	299.5 ± 1.0 299.5 ± 1.0	-54551 ± 150	1.3 ± 0.3 1.4 ± 0.2
10-mer	3	80	299.5 ± 1.0 299.5 ± 1.0	-54544 ± 150	1.5 ± 0.2
GG	4	80	299.5 ± 1.0 299.5 ± 1.0	-54548 ± 150	1.5 ± 0.5 2.2 ± 0.6
	1	80	299.7 ± 1.7	-21838 ± 94	-
	2	80	299.7 ± 1.7	-21835 ± 94	-
10-mer	3	80	299.7 ± 1.6	-21837 ± 94	-
	4	80	299.7 ± 1.7	-21837 ± 94	-
	1	80	299.7 ± 1.7	-20470 ± 91	-
10-mer	2	80	299.7 ± 1.7	-20473 ± 92	-
AA	3	80	299.7 ± 1.7	-20471 ± 91	-
	4	80	299.7 ± 1.7	-20471 ± 92	-
	1	80	299.7 ± 1.7	-20501 ± 92	-
10-mer	2	80	299.7 ± 1.7	-20501 ± 91	-
GG	3	80	299.7 ± 1.7	-20502 ± 91	-
	4	80	299.7 ± 1.7	-20502 ± 91	-

Supplementary Table S5. Convergence and stability data of MD simulations.