Supplementary Information S2 | **Biochemical Impact of Mutations in Dnmt3a found in Cancer Patients**

Residue (murine)	AA	Disease	Domain	Consequence	Ref
47 (44)	K		N-terminal	G9a/GLP methylation	[1]
308 (304)	Q	AML	PWWP	H3	[2]
333 (329)	D		PWWP	H3K36 (-)	[3]
337 (333)	S		PWWP	chromatin (-)	[4]
584 (580)	R		ADD	H3	[2]
640 (636)	F		Motif I	Cat	[5]
664 (660)	E	AML	Motif II	Cat	[5]
676 (672)	D		Motif III	AdoMet	[5]
710 (706)	C	sAML from MDS	Motif IV	Cat, DNA, AdoMet (-)	[5]
711 (707)	S		Motif V	Cat, AdoMet (-)	[5]
714 (710)	C	AML	Following motif IV	AdoMet	[5]
720 (716)	N	T-ALL	Following motif IV	Cat, DNA	[5]
721 (717)	R		Following motif IV	Cat	[5]
729 (725)	R	AML	Catalytic	DNA	[6]
733 (729)	E	AML, CMML	Catalytic	DNA	[6]
756 (752)	R		Motif VI	Cat (-),DNA (+)	[5]
757 (753)	K		Motif VI	Cat	[5]
771 (767)	R	AML, MDS, SM	Catalytic	DNA	[6]
792 (788)	R	T-ALL	Motif VIII	Cat, DNA (+)	[5]
826 (822)	K	MDS	Catalytic	DNAMult	[7]
831 (827)	R		Variable domain	DNA	[5]
836 (832)	R		Catalytic, Variable	DNAMult, DNA	[7], [5]
841 (837)	K	AML	Catalytic	DNAMult	[7]
844 (840)	K		Catalytic	Coop	[7]
845 (841)	D		Catalytic	DNA (+)	[7]
847 (843)	H		Catalytic	DNA (+)	[7]
855 (851)	K		Catalytic	Coop	[7]
856 (852)	E	T-ALL	Catalytic	DNA (+)	[7]
860 (856)	W	AML	Catalytic	Cat	[8]
873 (869)	H		Catalytic	Cat	[8]
876 (872)	D		Catalytic	Cat	[8]
879 (875)	N	AML	Catalytic	Cat	[8]
882 (878)	R	AML	In front of motif X	Cat, DNA	[5]

885 (881)	R	In front of motif X	Cat (-), AdoMet	[5]
887 (883)	R	Motif X	Cat, DNA	[5]

Analysis of amino acid residues tested for their DNA binding and/or catalytic activity. The human residue mutated in the indicated diseases, along with the mouse residue in which the functional consequences were tested, are indicated in the second column. A comprehensive summary of the role of additional residues is reported in Table S2. The indicated motifs are all part of the catalytic domain. Cat= reduced catalytic activity, Cat (-) = no catalytic activity; AdoMet= reduced AdoMet binding, AdoMet(-)=no AdoMet binding; DNA=reduced DNA binding; DNA(+)= enhanced DNA binding; DNAMulti= lose ability to multimerize on DNA; H3K36 (-)= lose H3K36 affinity; chromatin (-)= lose chromatin targeting; H3= insensitive to H3 peptide; Coop= lower cooperativity during multimerization; SM=systemic mastocytosis

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