Supplementary Information S1 | **Frequency of *DNMT3A* mutations in hematologic disorders and their associated clinical phenotypes.**

Disease	Patient population	Frequency (%)	Associated Clinical Characteristics	Ref
AML	De novo AML	62/281 (22.1)	Older age Higher WBC	1
	CN AML	44/120 (36.7)		
	De novo AML	51/200 (26)		2
	De novo AML	70/500 (14)	Older age Higher WBC Higher BM blast % Higher platelet count FAB M4/M5	3
	CN AML	51/223 (22.9)		
	De novo AML^	75/1185 (6.3)	Older age Higher WBC Higher BM blast % FAB M4/M5	4
	De novo AML excluding AML1-ETO, PML-RARa, and CBFβ-MYH11	73/605 (12.3)		
	De novo CN AML	70/194 (36.1)		5
	Intermediate cytogenetic risk AML	67/226 (29.6)	Female gender Higher WBC	6
	<60yrs AML (entire cohort)	87/498 (17.8)	Older age Higher WBC Higher platelet count FAB M4/M5	7
	De novo	81/447 (18.1)		
	sAML	6/51 (11.7)		
	<60yrs de novo AML	86/398 (23)		8
	<60yrs AML (entire cohort)	102/442 (23.1)	Older age Higher WBC Higher platelet count	9
	De novo	96/415		

		(23.1)		
	CN AML	72/194(37)		
	sAML	4/16 (25)		
	tAML	2/11 (18)		
	<60yrs AML (entire cohort)	370/1770 (20.9)	Older age Higher WBC Higher BM blast % Higher platelet count Female gender	10
	De novo AML	344/1243 (27.6)		
	CN AML	268/794 (33.7)		
	sAML	13/74 (17.6)		
	tAML	12/104 (11.5)		
	<60yrs CN AML	36/123 (29)	FAB M4/M5	11
	<60yrs CN AML	64/181 (35.5)	Higher WBC Higher BM blast % FAB M4/M5	12
	≥60yrs CN AML	77/234 (33.3)		
	AML FAB M1-M5	32/355 (9)	Older age Higher WBC FAB M4/M5	13
	FAB M1	0/6		
	FAB M2	0/77		
	FAB M3	0/94		
	FAB M4	9/66 (13.6)		
	FAB M5	23/112 (20.5)		
	sAML	13/37 (35) 10/27 (37) from MDS 3/10 (33) from MPN		14
	tAML	10/59 (17)		
	Pediatric AML	0/180 (0)		15
	Pediatric AML	3/140 (2.1)		16
	Pediatric AML	2/206 (1)		17
	Pediatric AML	0/135		18
MDS	De novo MDS	12/150 (8)	Older age	19
	De novo MDS	47/479 (9.8)	Older Age Higher platelet count	20

			Lower LDH	
	De novo MDS	26/221 (11.7)		21
	De novo MDS	15/115 (13)		5
	De novo MDS	127/944 (13.5)		22
	De novo MDS	5/193 (2.6)		23
	IPSS low and intermediate 1 risk MDS	36/288 (13)		24
	Pediatric MDS, tMDS	0/44**		25
MPN	MPN (entire cohort)	10/155 (9)		26
	PMF	1/16 (6)		
	PV	2/30 (7)		
	ET	0/30 (0)		
	Post MPN MF	2/4 (50)		
	Blast phase MPN	5/35 (14)		
	MPN (entire cohort)	3/149 (2)		27
	PV	1/30 (3.3)		
	ET	0/53 (0)		
	PMF	1/44 (2.3)		
	Blast phase MPN	1/14 (7.1)		
	Blast phase PMF	1/4 (25)		
	MPN (entire cohort)	3/94 (3.2)		28
	PMF	3/46 (7)		
	Post MPN MF	0/22 (0)		
	Blast phase MPN	0/11 (0)		
	PMF	28/483 (5.7)		29
	PMF (entire cohort)	3/64 (4.7)	Older age Higher WBC	30
	PMF	2/37 (5.4)		
	Post MPN MF	1/27 (3.7)		
	Post PV MF	1/13 (7.7)		
	Post ET MF	0/14 (0)		
	Blast phase MF	1/10 (10)		
	PV and ET	9/71 (12.6)		31
	Systemic Mastocytosis	3/26 (12)		32
	CML	0/79		33
	Blast crisis CML	0/81		34
CMML/JMML	CMML	0/15 (0)		28
	CMML-1	1/48 (2)		35 36
	CMML-2	1/16 (6.3)		
	sAML from CMML	6/23 (26)		
	JMML	0/49		
	CMML	5/227 (2)**		37
	CMML	7/103 (6.8)		5
	JMML	1/113 (0.8)		38

T cell leukemia/ lymphoma	T cell lymphoma	11/96 (11)		39
	PTCL	21/79 (26.6)		40
	PTCL-NOS	9/33 (27.3)		
	AITL	12/46 (26.1)		
	PTCL	10/53 (18.9)		41
	PTCL-NOS	2/17 (11.8)		
	AITL	7/30 (23.3)		
	ALCL ALK+	0/4		
	ALCL ALK-	1/2		
	Angioimmunoblastic T cell lymphoma (AITL)	28/85 (33.3)	Older age	42
	Adult T cell ALL (entire cohort)	16/83 (18)	Older age Lower Hgb	43
	Early T cell (Pro- and Pre-T cell ALL)	10/38 (26.3)		
	Cortical T cell ALL	5/39 (12.8)		
	Mature T cell ALL	0/3 (0)		
	Adult T cell ALL	17/99 (17)	Older age Lower Hgb	5
	Adult Early T cell Precursor ALL (ETP)	11/68 (16)	Older age	44
	Adult T cell ALL (entire cohort)	4/53 (7.5)		45
	Early immature T cell ALL[$]	4/28 (14)		
	Cortical T cell ALL[$]	0/25 (0)		
	Adult T cell ALL (entire cohort)	2/11 (18)		46
	ETP/Pro-/Pre-T cell ALL	2/ 7 (28.5)		
	Cortical/Medullary T cell ALL	0/4		
	Pediatric T cell ALL	0/91		18
	Pediatric ETP ALL	0/12		47
Mixed phenotype acute leukemia	Adult T/myeloid MPAL	10/18 (55.6)		48
	Pediatric mixed lineage leukemia	0/20 (0)		18

Cohorts smaller than 100 patients were excluded. The range of frequencies reported within a given disease type depends on the subset of patients examined as well as whether the entire *DNMT3A* gene or just the hotspots were examined. (A portion of these studies are also presented in Table 1 of the print version).

[^] Higher than expected rate of acute promyelocytic leukemia patients in entire cohort

[**] Only sequenced exon 23

[$] defined by gene expression signature

REFERENCES

1. Ley, T.J. et al. DNMT3A mutations in acute myeloid leukemia. *N Engl J Med* **363**, 2424-33 (2010).
2. Cancer Genome Atlas Research, N. Genomic and epigenomic landscapes of adult de novo acute myeloid leukemia. *N Engl J Med* **368**, 2059-74 (2013).
3. Hou, H.A. et al. DNMT3A mutations in acute myeloid leukemia-stability during disease evolution and the clinical implication. *Blood* (2011).
4. Shen, Y. et al. Gene mutation patterns and their prognostic impact in a cohort of 1,185 patients with acute myeloid leukemia. *Blood* (2011).
5. Roller, A. et al. Landmark analysis of DNMT3A mutations in hematological malignancies. *Leukemia* **27**, 1573-8 (2013).
6. Markova, J. et al. Prognostic impact of DNMT3A mutations in patients with intermediate cytogenetic risk profile acute myeloid leukemia. *Eur J Haematol* **88**, 128-35 (2012).
7. Thol, F. et al. Incidence and prognostic influence of DNMT3A mutations in acute myeloid leukemia. *J Clin Oncol* **29**, 2889-96 (2011).
8. Patel, J.P. et al. Prognostic relevance of integrated genetic profiling in acute myeloid leukemia. *N Engl J Med* **366**, 1079-89 (2012).
9. Ribeiro, A.F.T. et al. Mutant DNMT3A: a new marker of poor prognosis in acute myeloid leukemia. *Blood* **119**, 5824-5831 (2012).
10. Gaidzik, V.I. et al. Clinical impact of DNMT3A mutations in younger adult patients with acute myeloid leukemia: results of the AML Study Group (AMLSG). *Blood* **121**, 4769-77 (2013).
11. Renneville, A. et al. Prognostic significance of DNA methyltransferase 3A mutations in cytogenetically normal acute myeloid leukemia: a study by the Acute Leukemia French Association. *Leukemia* **26**, 1247-54 (2012).
12. Marcucci, G. et al. Age-related prognostic impact of different types of DNMT3A mutations in adults with primary cytogenetically normal acute myeloid leukemia. *J Clin Oncol* **30**, 742-50 (2012).
13. Yan, X.J. et al. Exome sequencing identifies somatic mutations of DNA methyltransferase gene DNMT3A in acute monocytic leukemia. *Nat Genet* **43**, 309-15 (2011).
14. Fried, I. et al. Frequency, onset and clinical impact of somatic DNMT3A mutations in therapy-related and secondary acute myeloid leukemia. *Haematologica* **97**, 246-50 (2012).
15. Ho, P.A. et al. Leukemic mutations in the methylation-associated genes DNMT3A and IDH2 are rare events in pediatric AML: a report from the Children's Oncology Group. *Pediatr Blood Cancer* **57**, 204-9 (2011).
16. Hollink, I.H.I.M. et al. Low frequency of DNMT3A mutations in pediatric AML, and the identification of the OCI-AML3 cell line as an in vitro model. **26**, 371-373 (2011).
17. Liang, D.C. et al. Cooperating gene mutations in childhood acute myeloid leukemia with special reference on mutations of ASXL1, TET2, IDH1, IDH2, and DNMT3A. *Blood* **121**, 2988-95 (2013).
18. Huether, R. et al. The landscape of somatic mutations in epigenetic regulators across 1,000 paediatric cancer genomes. *Nat Commun* **5**, 3630 (2014).
19. Walter, M.J. et al. Recurrent DNMT3A mutations in patients with myelodysplastic syndromes. *Leukemia* **25**, 1153-8 (2011).
20. Lin, C.C. et al. IDH mutations are closely associated with mutations of DNMT3A, ASXL1 and SRSF2 in patients with myelodysplastic syndromes and are stable during disease evolution. *Am J Hematol* **89**, 137-44 (2014).

21. Damm, F. et al. Mutations affecting mRNA splicing define distinct clinical phenotypes and correlate with patient outcome in myelodysplastic syndromes. *Blood* **119**, 3211-8 (2012).
22. Haferlach, T. et al. Landscape of genetic lesions in 944 patients with myelodysplastic syndromes. *Leukemia* **28**, 241-7 (2014).
23. Thol, F. et al. Rare occurence of DNMT3A mutations in myelodysplastic syndromes. *Haematologica* (2011).
24. Bejar, R. et al. Validation of a prognostic model and the impact of mutations in patients with lower-risk myelodysplastic syndromes. *J Clin Oncol* **30**, 3376-82 (2012).
25. Shiba, N. et al. DNMT3A mutations are rare in childhood acute myeloid leukaemia, myelodysplastic syndromes and juvenile myelomonocytic leukaemia. *Br J Haematol* **156**, 413-4 (2012).
26. Stegelmann, F. et al. DNMT3A mutations in myeloproliferative neoplasms. *Leukemia* **25**, 1217-9 (2011).
27. Brecqueville, M. et al. Mutation analysis of ASXL1, CBL, DNMT3A, IDH1, IDH2, JAK2, MPL, NF1, SF3B1, SUZ12, and TET2 in myeloproliferative neoplasms. *Genes Chromosomes Cancer* **51**, 743-55 (2012).
28. Abdel-Wahab, O. et al. DNMT3A mutational analysis in primary myelofibrosis, chronic myelomonocytic leukemia and advanced phases of myeloproliferative neoplasms. *Leukemia* **25**, 1219-20 (2011).
29. Vannucchi, A.M. et al. Mutations and prognosis in primary myelofibrosis. *Leukemia* **27**, 1861-9 (2013).
30. Brecqueville, M. et al. Array comparative genomic hybridization and sequencing of 23 genes in 80 patients with myelofibrosis at chronic or acute phase. *Haematologica* **99**, 37-45 (2014).
31. Quintas-Cardama, A. et al. Molecular analysis of patients with polycythemia vera or essential thrombocythemia receiving pegylated interferon alpha-2a. *Blood* **122**, 893-901 (2013).
32. Traina, F. et al. Single nucleotide polymorphism array lesions, TET2, DNMT3A, ASXL1 and CBL mutations are present in systemic mastocytosis. *PLoS One* **7**, e43090 (2012).
33. Lin, J. et al. Recurrent DNMT3A R882 mutations in Chinese patients with acute myeloid leukemia and myelodysplastic syndrome. *PLoS One* **6**, e26906 (2011).
34. Li, X. et al. Absence of DNMT3A gene mutation in chronic myeloid leukemia patients in blast crisis. *Eur J Haematol* **88**, 455-7 (2012).
35. Abu Kar, S. et al. Spliceosomal gene mutations are frequent events in the diverse mutational spectrum of chronic myelomonocytic leukemia but largely absent in juvenile myelomonocytic leukemia. *Haematologica* (2012).
36. Jankowska, A.M. et al. Mutational spectrum analysis of chronic myelomonocytic leukemia includes genes associated with epigenetic regulation: UTX, EZH2, and DNMT3A. *Blood* **118**, 3932-41 (2011).
37. Itzykson, R., Kosmider, O. & Fenaux, P. Somatic mutations and epigenetic abnormalities in myelodysplastic syndromes. *Best Pract Res Clin Haematol* **26**, 355-64 (2013).
38. Wlodarski, M.W. et al. Abnormal promoter DNA methylation in juvenile myelomonocytic leukemia is not caused by mutation in DNMT3A. *Blood* **118**, 4490-1 (2011).
39. Couronne, L., Bastard, C. & Bernard, O.A. TET2 and DNMT3A mutations in human T-cell lymphoma. *N Engl J Med* **366**, 95-6 (2012).
40. Sakata-Yanagimoto, M. et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet* **46**, 171-5 (2014).
41. Palomero, T. et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet* **46**, 166-70 (2014).

42. Odejide, O. et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood* **123**, 1293-6 (2014).
43. Grossmann, V. et al. The molecular profile of adult T-cell acute lymphoblastic leukemia: mutations in RUNX1 and DNMT3A are associated with poor prognosis in T-ALL. *Genes Chromosomes Cancer* **52**, 410-22 (2013).
44. Neumann, M. et al. Whole-exome sequencing in adult ETP-ALL reveals a high rate of DNMT3A mutations. *Blood* **121**, 4749-52 (2013).
45. Van Vlierberghe, P. et al. Prognostic relevance of integrated genetic profiling in adult T-cell acute lymphoblastic leukemia. *Blood* **122**, 74-82 (2013).
46. Simon, C. et al. A key role for EZH2 and associated genes in mouse and human adult T-cell acute leukemia. *Genes Dev* **26**, 651-6 (2012).
47. Zhang, J. et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. *Nature* **481**, 157-63 (2012).
48. Kern, W. et al. Mixed Phenotype Acute Leukemia, T/Myeloid, NOS (MPAL-TM) Has a High DNMT3A Mutation Frequency and Carries Further Genetic Features of Both AML and T-ALL: Results of a Comprehensive Next-Generation Sequencing Study Analyzing 32 Genes. *Blood* **120**, 403 (2012).