

Table S1. 95 targeted genes and exons.

	Gene	Exon
1	<i>ABL1</i>	e2-e10
2	<i>ASXL1</i>	e1-e13
3	<i>ATM</i>	e2-e63
4	<i>BCL11B</i>	e4
5	<i>BCOR</i>	e2-e15
6	<i>BCORL1</i>	e1-e12
7	<i>BRAF</i>	e15
8	<i>BRCC3</i>	e3-e11
9	<i>CALR</i>	e9
10	<i>CBL</i>	e7-e8
11	<i>CBLB</i>	e9-e11
12	<i>CD79B</i>	e5-e6
13	<i>CEBPA</i>	e1
14	<i>CNOT3</i>	e1-e2
15	<i>CREBBP</i>	e2-e21, e23-31
16	<i>CRLF2</i>	e6
17	<i>CSF1R</i>	e22
18	<i>CSF3R</i>	e14-e18
19	<i>CTCF</i>	e3-e12
20	<i>CTNNB1</i>	e2-e4
21	<i>CUX1</i>	e1-e21
22	<i>CXCR4</i>	e2
23	<i>DNMT3A</i>	e2-e23
24	<i>DNMT3B</i>	e2-e23
25	<i>EED</i>	e1-e12
26	<i>EGFR</i>	e18-e21
27	<i>EP300</i>	e18-e27
28	<i>ETV6</i>	e1-e8
29	<i>EZH2</i>	e2-e8, e11-e20
30	<i>FANCL</i>	e1-e14
31	<i>FBXW7</i>	e8-e12
32	<i>FLT3</i>	e14-e16, e20
33	<i>GATA1</i>	e2-e6
34	<i>GATA2</i>	e2-e6
35	<i>GATA3</i>	e4-e6
36	<i>GNAS</i>	e8-e9
37	<i>GNB1</i>	e5-e6
38	<i>IDH1</i>	e4
39	<i>IDH2</i>	e4
40	<i>IKZF1</i>	e2-e8
41	<i>IKZF2</i>	e1-e8
42	<i>IKZF3</i>	e1-e8
43	<i>IL7R</i>	e6

44	<i>JAK1</i>	e10-e25
45	<i>JAK2</i>	e12, e14
46	<i>JAK3</i>	e11-e24
47	<i>KIT</i>	e8-9, e11, e17
48	<i>KRAS</i>	e2-e5
49	<i>LUC7L2</i>	e3-e11
50	<i>MAP2K1</i>	e2-e3
51	<i>MEF2B</i>	e3
52	<i>MPL</i>	e10
53	<i>MYD88</i>	e5
54	<i>NOTCH1</i>	e24-e28, e34
55	<i>NOTCH2</i>	e24-e28, e34
56	<i>NOTCH3</i>	e25-e26, e33
57	<i>NPM1</i>	e10-e11
58	<i>NRAS</i>	e2-e5
59	<i>NT5C2</i>	e9, e11, e13, e15, e17
60	<i>PAX5</i>	e3, e6-e7
61	<i>PDGFRA</i>	e10-e21, e23
62	<i>PDS5B</i>	e3-e35
63	<i>PHF6</i>	e2-e10
64	<i>PIGA</i>	e2-e6
65	<i>PIK3CA</i>	e2, e10, e21
66	<i>PIM1</i>	e1-e6
67	<i>PRPF40B</i>	e2-e26
68	<i>PRPF8</i>	e2-e43
69	<i>PTEN</i>	e1-e9
70	<i>PTPN11</i>	e1-e15
71	<i>RAD21</i>	e2-e14
72	<i>RET</i>	e7
73	<i>RIT1</i>	e1-e6
74	<i>RPL10</i>	e5
75	<i>RUNX1</i>	e2-e9
76	<i>SETBP1</i>	e4
77	<i>SETD2</i>	e1-e4, e6-e21
78	<i>SF1</i>	e1-e10, e13
79	<i>SF3A1</i>	e1-e2, e5-e16
80	<i>SF3B1</i>	e12-e16
81	<i>SH2B3</i>	e2-e8
82	<i>SMC1A</i>	e1-e25
83	<i>SMC3</i>	e2-e29
84	<i>SRSF2</i>	e1
85	<i>STAG2</i>	e3-e35
86	<i>STAT3</i>	e2-e17, e21-23
87	<i>TET2</i>	e3-e11
88	<i>TLR2</i>	e1
89	<i>TP53</i>	e2-e11
90	<i>U2AF1</i>	e2, e6

91	<i>U2AF2</i>	e1-e12
92	<i>WHSC1</i>	e17-e18
93	<i>WT1</i>	e1-e10
94	<i>XPO1</i>	e15-e16
95	<i>ZRSR2</i>	e1-e11

Table S2. Clinicopathologic details of patients with non-SH2 domain *STAT3* variants.

	NGS Indication	Specimen	Tissue involvement (%)	Lymphoid cells present on marrow aspirate	Status-post allo-transplant	Variant (variant allele fraction)	<i>STAT3</i> domain localization	<i>STAT3</i> population frequency (ExAC Browser) Lek M et al. <i>Nature</i> . 2016. 536:285–291. (accessed 8-20-2017)	<i>STAT3</i> population frequency (gnomAD Browser) Lek M et al. <i>Nature</i> . 2016. 536:285–291. (accessed 8-20-2017)
Somatic <i>STAT3</i> mutations	Chronic lymphocytic leukemia	Blood	98%	N/A	No	<i>STAT3</i> c.172G>A p.H58Y (28.9%) CNOT3 c.58G>A p.E20K (16.5%)	N-terminal	No	No
	Macrocytic anemia	Marrow	N/A	15%	No	<i>STAT3</i> c.514delC p.D171fs* (22.3%)	Coiled-coil	No	No
	BPDCN	Blood	ND	N/A	No	<i>STAT3</i> c.718C>G p.L240V (35.4%)	Coiled-coil	No	No
	Acute myeloid leukemia	Marrow	27%	24%	No	<i>STAT3</i> c.1145G>A p.R382Q (6.7%) EZH2 c.2069G>A p.R690H (21.0%) RIT1 c.104G>C p.S35T (11.2%)	DNA-binding	No	No
	Primary myelofibrosis	Marrow	N/A	6%	No	<i>STAT3</i> c.2060C>T p.C687Y (10.1%) JAK2 c.1849G>T p.V617F (35.7%)	SH2-TA border	1 of 121,410	No
Variant allele fraction, and population allele frequency)	Chronic lymphocytic leukemia	Marrow	90%	N/A	Yes	<i>STAT3</i> c.62T>C p.L21P (3.1%)	N-terminal	No	No
	Myelodysplastic syndrome	Marrow	N/A	N/A	No	<i>STAT3</i> c.137G>A p.A46V (50.0%) SRSF2 c.284G>T p.P95H (58.2%) STAG2 c.1002G>A p.W334* (24.8%) STAG2 c.2325C>G p.Y775* (6.0%) STAG2 c.1096_1097insT p.L366fs* (9.6%) RUNX1 c.493C>T p.G165S (42.5%)	N-terminal	No	No
	Leukopenia, thrombocytopenia	Blood	N/A	N/A	No	<i>STAT3</i> c.361A>T p.T121S (56.6%)	N-terminal	No	1 of 231,666
	Acute myeloid leukemia	Blood	ND	N/A	Yes	<i>STAT3</i> c.562G>T p.L188M (27.5%) ASXL1 c.2175delA p.R725fs* (23.4%) SRSF2 c.284G>A p.P95L (24.1%) TET2 c.4105T>C p.S1369P (26.8%) TET2 c.5654C>T p.P1885L (17.8%)	Coiled-coil	2 of 120,756	18 of 276,848
	Acute myeloid leukemia	Marrow	83%	N/A	Yes	<i>STAT3</i> c.581C>T p.S194L (10.1%) NPM1 c.863_864insCCGA p.W288fs*10 (43.9%) TP53 c.524G>A p.R175H (80.7%) TET2 c.3679G>T p.V1227L (7.2%) PRPF8 c.4808C>A p.A1603E (26.7%)	Coiled-coil	No	1 of 246,012

Presumed germline STAT3 variants (based on domain localization, variant allele frequency)	Variant Information				Variant Details		Variant Frequency		
	Disease	Tissue	Prevalence	Allele Frequency	Variant	Protein Domain	Variant Count	Allele Count	Total Count
Mast cell activation syndrome	Marrow	N/A	N/A	No	STAT3 c.594G>C p.Q198H (60.7%) KRAS c.35G>A p.G12D (3.3%)	Coiled-coil	1 of 121,226	3 of 246,078	
LGL leukemia	Blood	26%	N/A	No	STAT3 c.832C>T p.R278C (48.2%) STAT3 c.1940A>T p.N647I (14.1%)*	Coiled-coil	No	No	
Multiple myeloma	Marrow	12%	N/A	No	STAT3 c.900G>T p.Q300H (51.4%)	Coiled-coil	No	1 of 246,264	
Pancytopenia	Blood	N/A	N/A	No	STAT3 c.1381C>G p.V461L (52.5%)	DNA-binding	515 of 121,306	1698 of 277,040	
Acute myeloid leukemia	Marrow	85%	N/A	No	STAT3 c.1381G>C p.V461L (53.2%)	DNA-binding	515 of 121,306	1698 of 277,040	
MSD/MPN	Marrow	N/A	N/A	No	STAT3 c.1381G>C p.V461L (48.5%)	DNA-binding	515 of 121,306	1698 of 277,040	
Lymphoplasmacytic lymphoma	Marrow	34%	N/A	No	STAT3 c.1381G>C p.V461L (50.2%) MYD88 c.794T>C p.L265P (2.7%) CXCR4 c.1000C>T p.R338* (5.7%)	DNA-binding	515 of 121,306	1698 of 277,040	
B-lymphoblastic lymphoma	Blood	ND	N/A	No	STAT3 c.1492T>C p.I498V (47.9%)	Linker	42 of 121,404	78 of 277,222	
Acute myeloid leukemia	Marrow	82%	N/A	No	STAT3 c.2050G>C p.G684R (44.1%) DNMT3A c.2645G>A p.R882H (31.9%) TP53 c.844C>T p.R282W (29.9%)	TA	7 of 121,412	15 of 277,230	
Leukocytosis, splenomegaly	Blood	N/A	N/A	No	STAT3 c.2082T>A p.H694Q (49.4%)	TA	8 of 121,404	23 of 277,244	
Acute myeloid leukemia	Blood	75%	N/A	No	STAT3 c.2174C>T p.P725L (56.5%) BCORL1 c.3895C>T p.R1299* (94.7%) DNMT3A c.2644C>T p.R882C (46.4%) IDH1 c.394C>T p.R132C (46.1%) STAG2 c.775C>T p.R259* (84.0%) WT1 c.1288C>T p.R362* (47.2%) DNMT3A c.2645G>A p.R882H (15.2%) TP53 c.637C>T p.R213* (5.9%)	TA	1 of 120,632	1 of 245,438	
Leukocytosis, thrombocytopenia	Blood	N/A	N/A	No	STAT3 c.2174G>A p.P725L (61.5%) DNMT3A c.1227C>T p.W409* (41.3%)	TA	1 of 120,632	1 of 245,438	
Flushing	Blood	N/A	N/A	No	STAT3 c.2228G>T p.G743V (68.8%)	TA	20 of 121,266	35 of 277,048	

N/A, not applicable; ND, no data; TA, transactivation
BPDCN, blastic plasmacytoid dendritic cell neoplasm
MDS/MPN, myelodysplastic/myeloproliferative neoplasm
*Somatic mutation