Clinical and biological impact of ATP-binding cassette transporter activity in adult acute myeloid leukemia

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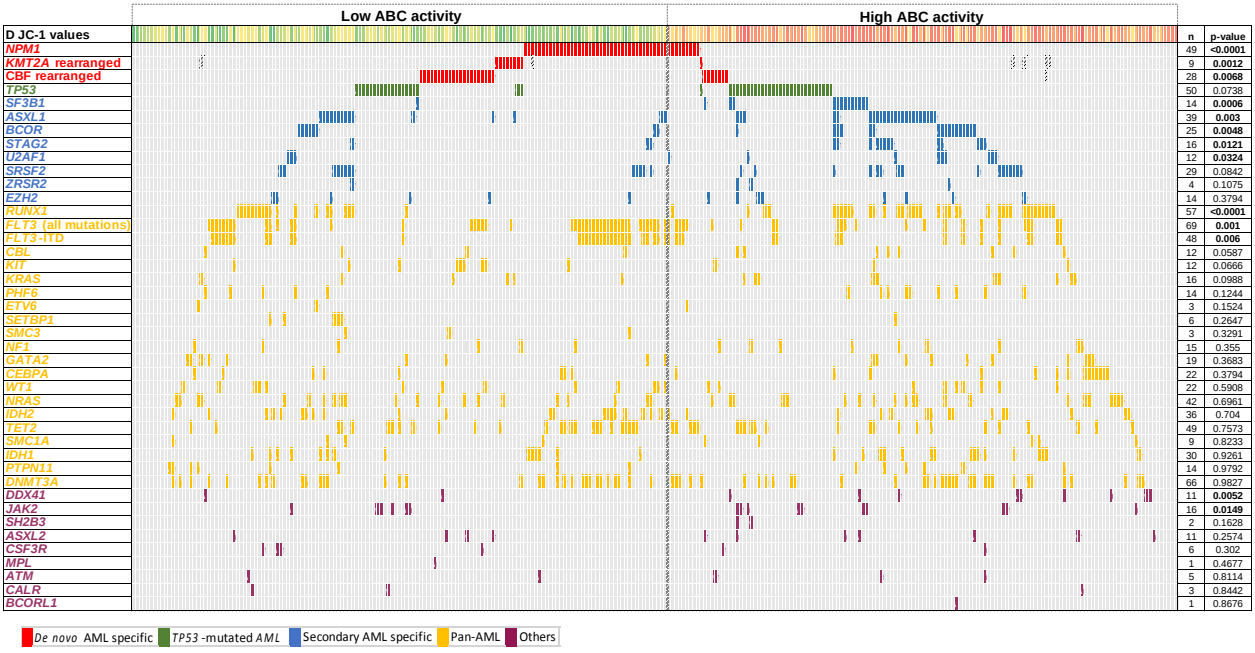
SUPPLEMENTARY DATA

Supplementary Table 1. Flow cytometry features according to ATP-binding cassette (ABC) activity for each analyzed marker.

Marker	n	Low ABC activity (median, %)	Low ABC activity (standard error)	High ABC activity (median, %)	High ABC activity (standard error)	p-value
CD34	357	72	2.73	87	2.31	**<0.0001**
CD117	356	89	1.65	97	1.4	**<0.0001**
CD33	356	95	1.3	87	2.3	**0.0338**
CD13	353	89	2.1	93	1.95	**0.0013**
CD64	348	17	1.78	4	1.42	**<0.0001**
HLA-DR	347	82	2.55	91	2.3	**<0.0001**
CD36	347	5	1.45	3	1.64	0.1087
CD14	345	0	0.46	0	0.13	**0.0107**
CD4	343	8	1.97	2	1.53	**0.0107**
CD19	342	0	1.15	0	0.37	0.0863
cyMPO	341	79	2.72	22	2.95	**<0.0001**
CD56	341	0	2.08	0	2.12	0.7469
CD2	331	0	0.66	0	0.53	0.3147
cyCD3	328	0	0.22	0	0.36	0.7781
cyCD79a	267	0	1.06	0	0.71	0.2795
CD7	235	2	2.28	5	3.48	0.363
CD3	204	0	0.08	0	0.02	0.0907
CD15	155	25	2.32	14	2.48	**0.0325**
CD11b	152	6	2.35	6	3.8	0.9673
CD22	137	0	0.51	0	1.89	0.9427
CD10	133	0	1.43	0	0.41	0.2576
CD5	115	0	0.93	0	0.73	0.476
CD65	68	10	4.53	1	1.77	**0.0122**

p-value <0.05 are in bold.



Supplementary Figure 1. **Co-mutation table for patients with available next-generation sequencing data.**

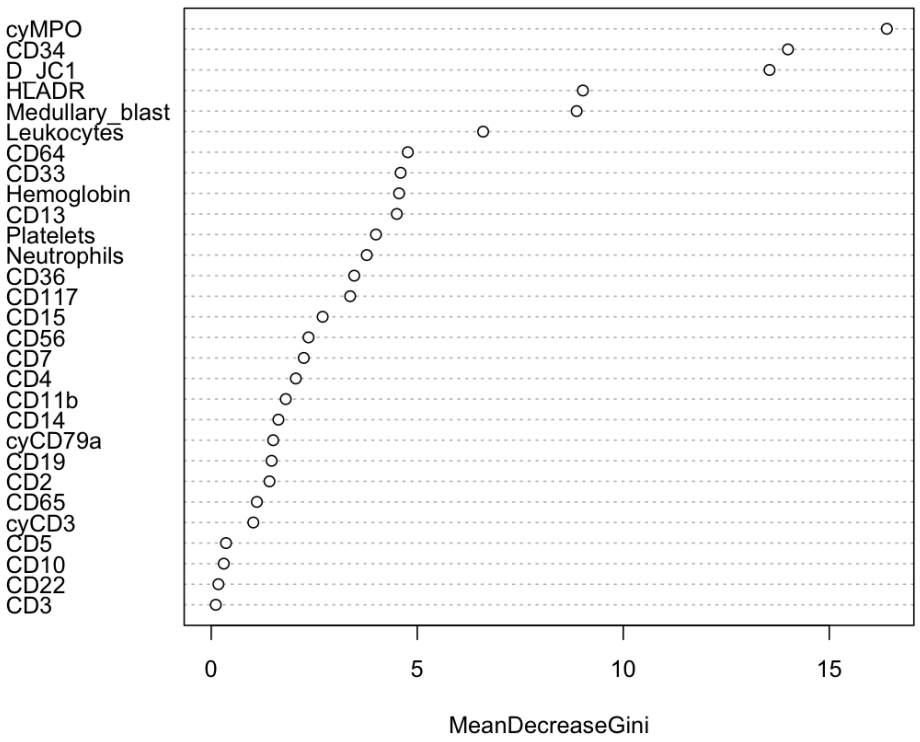
Mutations are represented by colored bars and each column represents one of the 291 sequenced subjects. D JC-1 values are at the top of the Figure: red and green color gradient according to forty genes and *KMT2A* and CBF rearrangements were grouped following the Lindsley classification. Colors reflect ontogeny specificity of mutated genes and cytogenetic abnormalities: *de novo* AML specific (red), *TP53*-mutated AML (green), secondary AML specific (blue), pan-AML (yellow) and others (burgundy). The number of patients with mutations for each gene and p-value of the ABC^{low} and ABC^{high} group comparisons are shown on the right. Not available data are hatched. *CEBPA* biallelic mutations are represented in dark yellow. p-values <0.05 are in bold.

Supplementary Table 2. Molecular biology features according to ATP-binding cassette (ABC) activity.

Genes	Mutated genes ABC^{low} (n)	Mutated genes ABC^{low} (frequency)	Mutated genes ABC^{high} (n)	Mutated genes ABC^{high} (frequency)	p-value
NPM1	50	83%	10	17%	**<0.0001**
***KMT2A* rearranged**	9	82%	2	18%	**0.0075**
CBF rearranged	24	77%	7	23%	**0.0148**
TP53	20	40%	30	60%	0.0738
SF3B1	1	7%	13	93%	**0.0006**
ASXL1	15	38%	24	62%	**0.0030**
BCOR	8	32%	17	68%	**0.0048**
STAG2	3	19%	13	81%	**0.0121**
U2AF1	3	25%	9	75%	**0.0324**
SRSF2	13	45%	16	55%	0.0842
ZRSR2	1	25%	3	75%	0.1075
EZH2	6	43%	8	57%	0.3794
RUNX1	19	33%	38	67%	**<0.0001**
FLT3 (all mutations)	51	66%	26	34%	**0.0034**
FLT3-ITD	38	68%	18	32%	**0.0096**
CBL	4	33%	8	67%	0.0587
KIT	9	75%	3	25%	0.0666
KRAS	6	38%	10	63%	0.0988
PHF6	5	36%	9	64%	0.1244
ETV6	2	67%	1	33%	0.1524
CEBPA	9	39%	14	61%	0.238
SETBP1	5	83%	1	17%	0.2647
SMC3	3	100%	0	0%	0.3291
NF1	6	40%	9	60%	0.355
GATA2	9	47%	10	53%	0.3683
WT1	13	59%	9	41%	0.5908
IDH2	22	59%	15	41%	0.6273
NRAS	21	50%	21	50%	0.6961
TET2	26	53%	23	47%	0.7573
SMC1A	4	44%	5	56%	0.8233
IDH1	14	47%	16	53%	0.9261
PTPN11	8	57%	6	43%	0.9792

DNMT3A	32	48%	34	52%	0.9827
DDX41	2	18%	9	82%	**0.0052**
JAK2	6	38%	10	63%	**0.0149**
SH2B3	0	0%	2	100%	0.1628
ASXL2	4	36%	7	64%	0.2574
CSF3R	4	67%	2	33%	0.302
MPL	1	100%	0	0%	0.4677
ATM	2	40%	3	60%	0.8114
CALR	2	67%	1	33%	0.8442
BCORL1	0	0%	1	100%	0.8676

p-values <0.05 are in bold.



Supplementary Figure 2. Random Forest variable importance plot to predict *de novo* ontogeny.

Variables are ranked in terms of importance (Y axis) (with variables of highest importance at the top), with mean decrease in Gini coefficient (X axis). Mean decrease in Gini coefficient shows how each variable contributes to the homogeneity of nodes in the Random Forest model. A higher decrease in Gini coefficient implies that the variable plays a greater role in the classification process.

Supplementary Table 3. mRNA expression of two ATP-binding cassette transporters according to gene mutations of an acute myeloid leukemia cohort (Acute Myeloid Leukemia (OHSU, Nature 2018)).

			mRNA expression *ABCB1*			mRNA expression *ABCG2*		
Genes	**Mutated patients (n)**	**Wild-type patients (n)**	**Mutated patients (median)**	**Wild-type patients (median)**	**p-value**	**Mutated patients (median)**	**Wild-type patients (median)**	**p-value**
NPM1	82	323	2.007	10.69	**<0.0001**	0.1374	0.478	**<0.0001**
TP53	35	370	22.78	6.562	**<0.0001**	1.135	0.3046	**<0.0001**
FLT3	122	283	3.628	9.889	**<0.0001**	0.199	0.445	**0.0001**
NRAS	60	345	5.68	7.591	0.2974	0.3463	0.3151	0.9435
PHF6	14	391	12.69	6.969	0.0902	1.595	0.3151	**0.0006**
JAK2	14	391	20.98	6.969	**0.0244**	1.469	0.3188	**0.0021**
IDH2	43	362	8.207	7.004	0.4585	0.3074	0.342	0.7052
SF3B1	21	384	8.679	7.004	0.257	0.4107	0.3315	0.623
ZRSR2	43	362	12.33	6.873	0.7456	0.445	0.3334	0.2952
BCORL1	9	396	31.27	6.983	**0.0274**	1.03	0.3295	0.1237
IDH1	34	371	5.453	7.464	0.6656	0.1867	0.3485	0.186
WT1	34	371	6.094	7.328	0.5994	0.5829	0.3276	0.4507
CEBPA	26	379	40.53	6.542	**<0.0001**	0.8119	0.3074	**0.0115**
DNMT3A	85	320	4.043	8.094	0.0521	0.2146	0.3659	**0.0119**
PTPN11	22	383	2.945	7.591	0.1325	0.2809	0.3409	0.439
STAG2	22	383	11.24	7.012	0.4512	0.5212	0.3355	0.4434
TET2	50	355	7.887	7.012	0.9236	0.2787	0.3495	0.4786
KRAS	19	386	10.41	7.026	0.7296	0.2655	0.3433	0.4431
GATA2	18	387	50.01	6.582	**<0.0001**	0.8128	0.3095	**0.0123**
U2AF1	18	387	13.49	7.012	0.1692	0.6953	0.3355	0.4375
EZH2	16	389	8.368	7.04	0.4472	0.2898	0.3409	0.8485
SRSF2	43	362	12.33	6.873	**0.0194**	0.6765	0.3068	**0.0133**
NF1	4	401	22.54	7.04	0.2267	2.524	0.3314	**0.0233**
RUNX1	52	353	10.97	6.79	**0.0405**	0.495	0.3151	**0.0267**
KIT	9	396	6.955	7.376	0.7543	0.2019	0.342	0.3268
ASXL1	8	397	7.322	7.328	0.8619	0.2991	0.3492	0.9234
CSF3R	8	397	7.322	7.328	0.8188	0.9442	0.3385	0.4268
SMC3	8	397	1.427	7.424	0.1971	0.6892	0.3355	0.6093
CBL	7	398	5.31	7.376	0.7632	0.2599	0.342	0.1404
BCOR	25	380	23.89	6.873	**0.0074**	0.6881	0.3169	**0.0405**
CALR	3	402	10.6	7.184	0.8029	0.163	0.3397	0.9388

KMT2A	3	402	9.413	7.184	0.8357	0.4063	0.337	0.4227
MPL	3	402	13.54	7.026	0.3471	0.4815	0.337	0.4696
SETBP1	3	402	4.809	7.376	0.3497	0.3031	0.3397	0.8284
DDX41	2	403	24.63	7.04	0.3639	0.2834	0.3385	0.385
ETV6	2	403	26.93	7.04	0.1808	0.2427	0.3409	0.6737
ASXL2	1	404	NA	NA	NA	NA	NA	NA
ATM	1	404	NA	NA	NA	NA	NA	NA
SH2B3	0	405	NA	NA	NA	NA	NA	NA

p-values <0.05 are in bold.

Supplementary Table 4. Univariate and multivariate analyses for event-free survival with data censoring at the time of allogeneic-HSC transplantation.

Variable	Univariate p-value	Multivariate HR (95% CI)	p-value
Age	**0.0059**	1.010 (0.995-1.024)	0.1889
Cytogenetics status (poor *vs.* other)	**<0.0001**	3.529 (2.170-5.739)	**<0.0001**
CEBPA biallelic mutation	**0.0269**	0.380 (0.089-1.629)	0.1926
ASXL1^{mut}	**0.0025**	1.993 (1.046-3.796)	**0.0359**
DNMT3A^{mut}	**0.0069**	2.201 (1.385-3.497)	**0.0008**
U2AF1^{mut}	**0.003**	2.817 (1.168-6.795)	**0.0211**
PHF6^{mut}	**<0.0001**	4.088 (1.601-10.438)	**0.0032**
CBL^{mut}	**0,0004**	3.961 (1.117-14.045)	**0.0330**
SETBP1^{mut}	**<0.0001**	12.756 (3.958-41.109)	**<0.0001**
ABC activity	0.09	2.269 (1.050-4.901)	**0.0370**

HR: hazard ratio. Only data with p-values <0.1 in univariate analyses are represented.