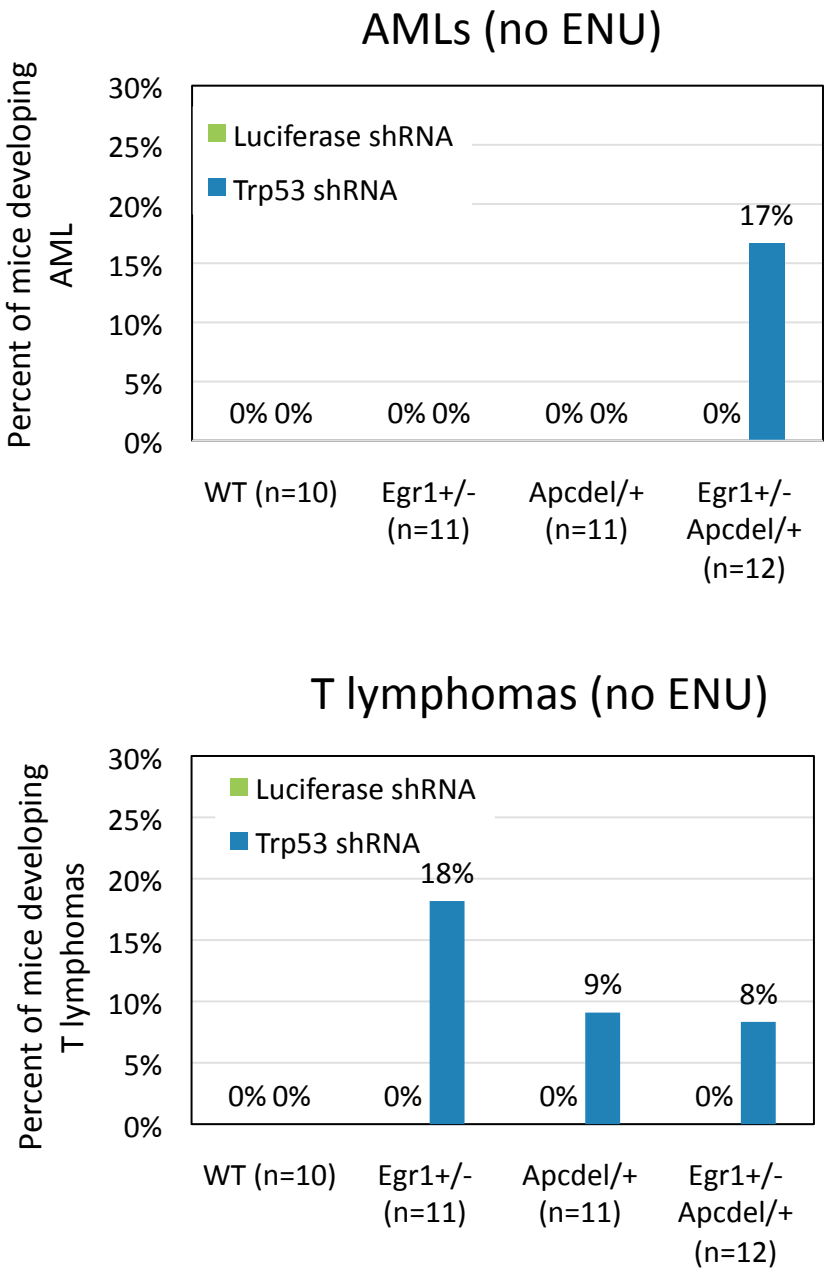


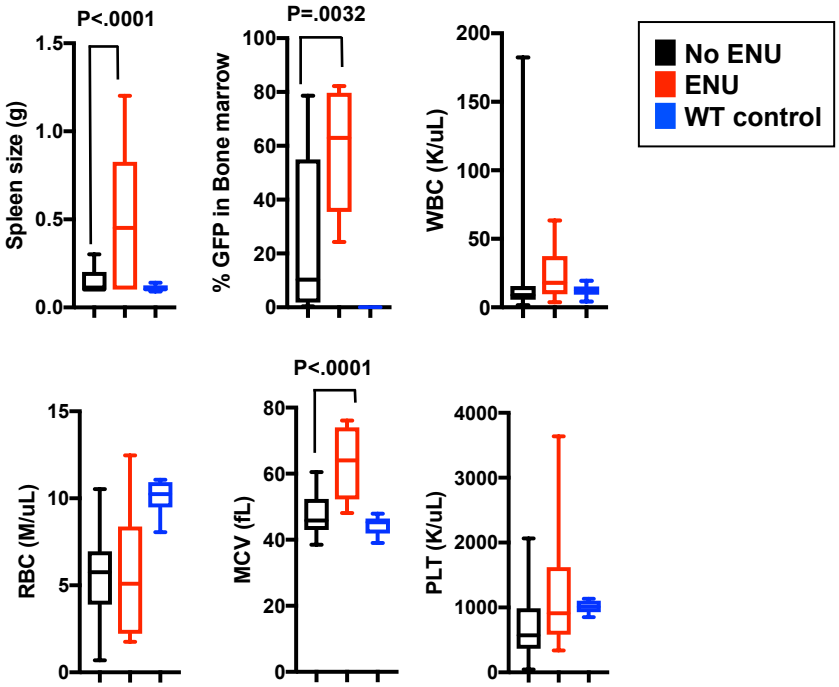
Supplemental Figure 1. Cell intrinsic haploinsufficinet loss of *Egr1*, *Apc* with *Trp53* knockdown promotes AML at a low frequency in the absence of ENU. *Egr1*$^{+/+}$ *(WT); Egr1*$^{+/-}$*; Apc*$^{del/+}$ *; or Egr1*$^{+/-}$*,Apc*$^{del/+}$ bone marrow was transduced with luciferase (control) or *Trp53* shRNA and transplanted into lethally irradiated WT recipients and monitored for disease (previously published Stoddart et al., 2014). The percent of mice developing AML (upper panel) and T lymphomas (lower panel) is shown. AML development was only observed with loss of *Egr1*, *Apc* and *Trp53*.

A

ENU treated mice

Mouse	Survival (days)	Disease Equivalent	Myeloid Blasts (%)	Transplantable
6322	234	T lymphoma	NA	ND
6362	199	T lymphoma	NA	ND
6333	151	MDS, RAEB-1; T lymphoma	6%	ND
7089	102	MDS, RAEB-1; T lymphoma	9%	ND
6327	139	MDS, RAEB-2	18%	No
7104	263	MDS, RAEB-2; T lymphoma	19%	ND
6323	356	AML	28%	No
7074	382	AML	30%	Yes
7103	157	AML	68%	Yes
7101	200	AML	78%	Yes
7105	327	AML	>20%	ND

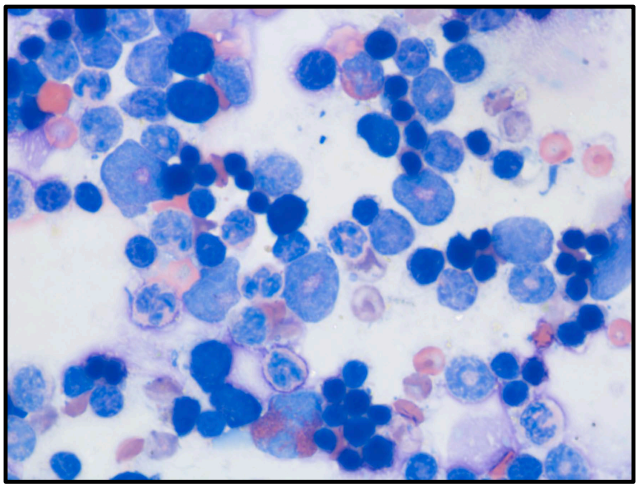
B



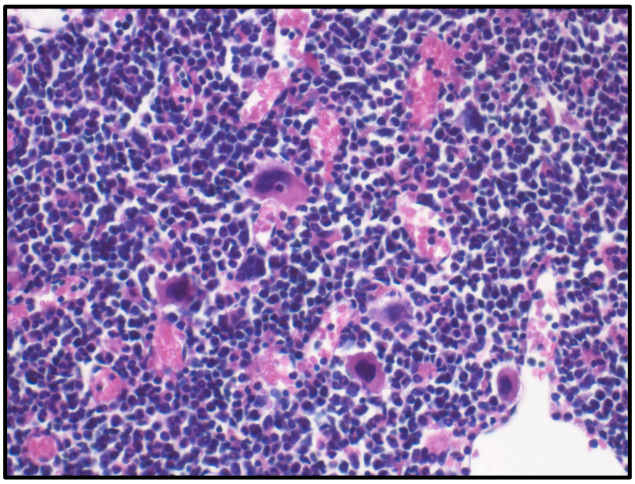
Supplemental Figure 2. Hematological parameters in ENU-treated mice and in mice without ENU treatment. *Egr1*$^{+/-}$, *Apc*$^{del/+}$ bone marrow cells were transduced with *Trp53* shRNA, and transplanted into lethally-irradiated WT recipient mice. ENU treatment is described in Fig. 1 **(A)** A summary of the characteristics of the ENU-treated mice and the human equivalent disease. NA, not applicable; ND, not determined. About half of the ENU-treated mice developed AML (>20% myeloid blasts), and ~40% developed MDS. **(B)** At the time of sacrifice, spleen weights, percent of GFP^{+} cells in the BM, white blood cell (WBC) counts, red blood cell (RBC) counts, mean cell volume (MCV) and platelet (PLT) counts were plotted for both groups. Healthy WT control mice are shown for comparison. The average spleen size and percent of *Trp53* shRNA^{+} (GFP^{+}) bone marrow cells was higher in ENU treated mice, reflective of the fact that most ENU-treated mice developed splenomegaly and had expansion of *Trp53* shRNA^{+} malignant cells .

WT control mouse

Bone marrow smear

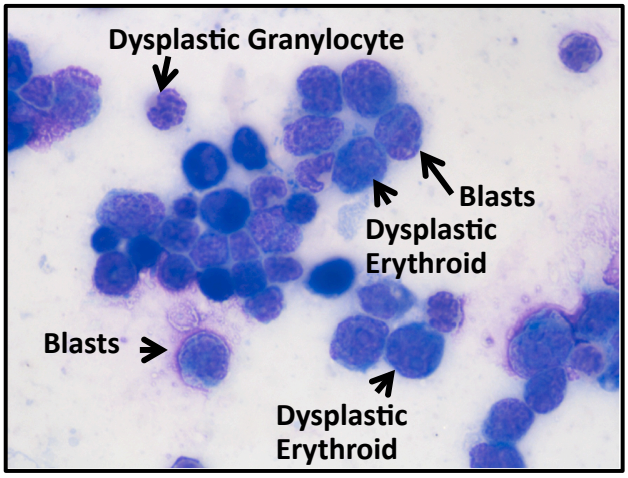


Bone core biopsy

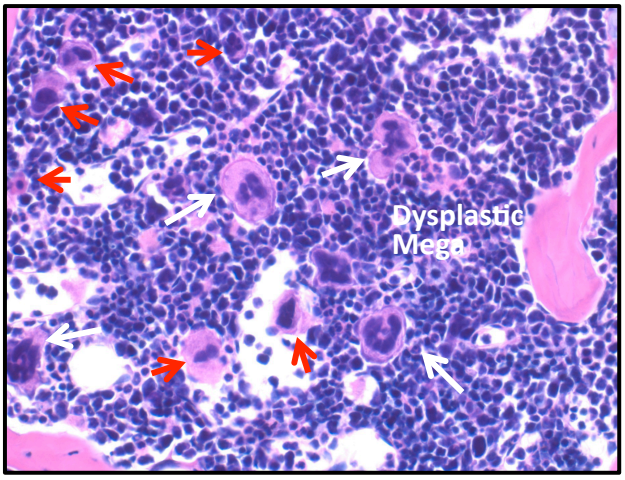


Egr1$^{+/-}$, *Apc* $^{del/+}$, *Trp53* shRNA → WT recipient (ENU-both)

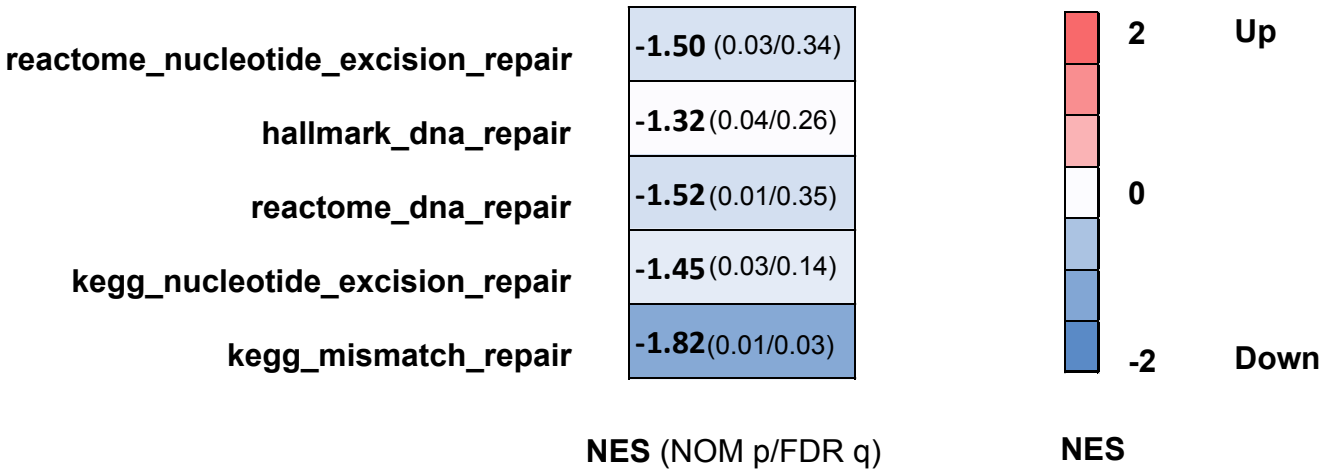
Bone marrow smear



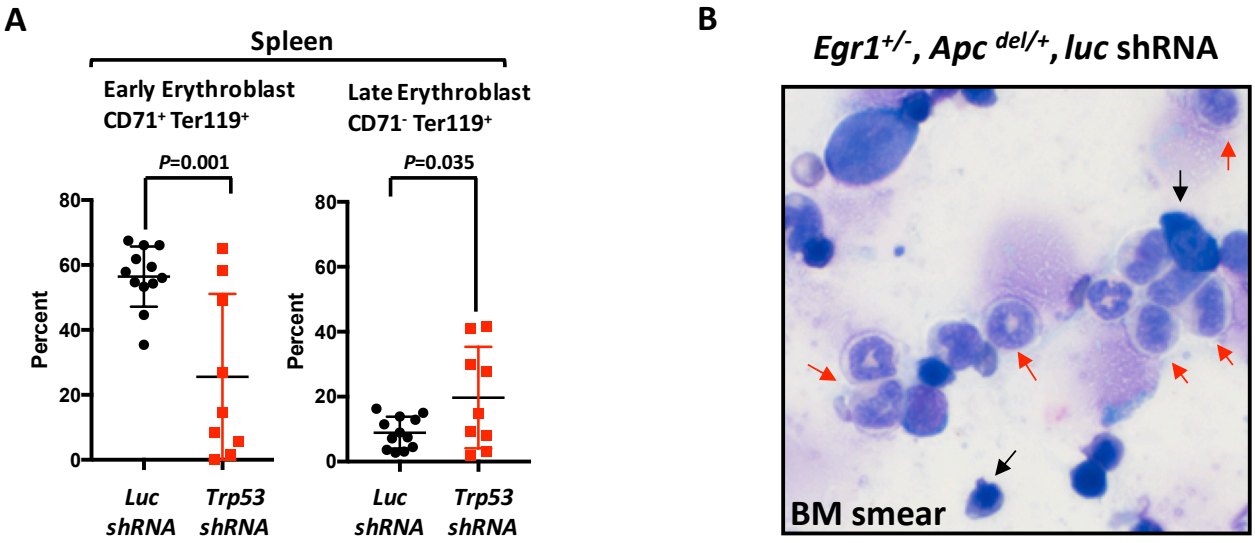
Bone core biopsy



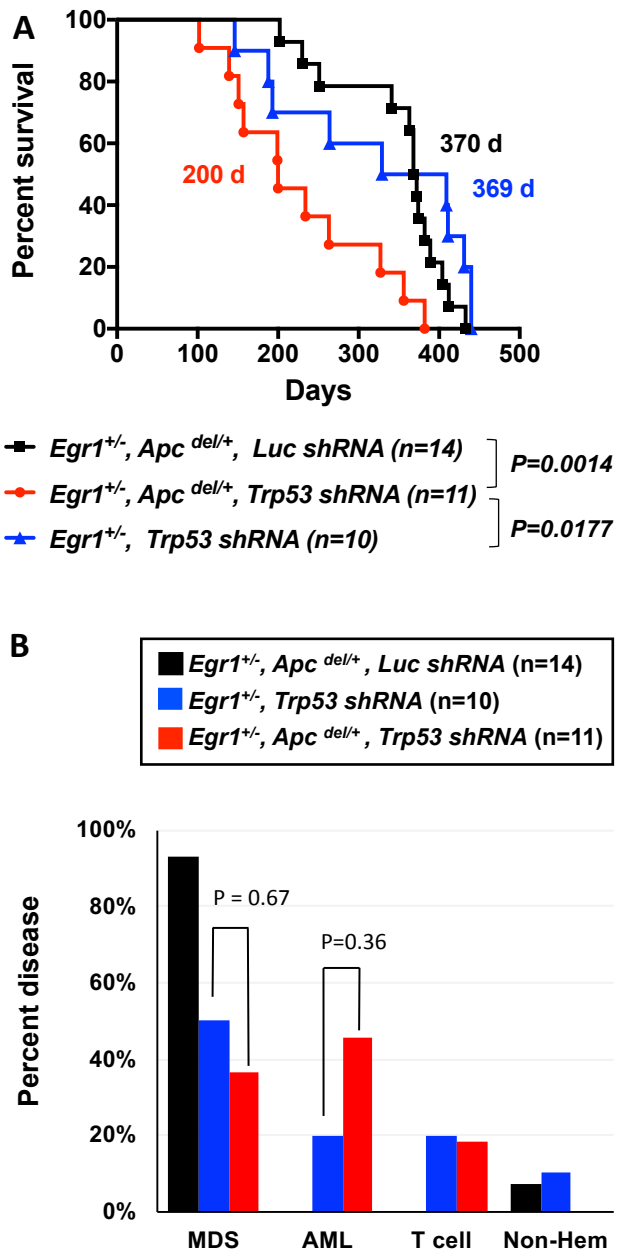
Supplemental Figure 3. Mouse myeloid neoplasms with *Trp53* loss exhibit trilineage dysplasia. An example of a WT recipient of *Egr1*$^{+/-}$, *Apc*$^{del/+}$ bone marrow transduced with *Trp53* shRNA (ENU-both) that exhibits dysplasia of erythroid and myeloid cells, and megakaryocytes is shown. Blasts, dysplastic erythroid cells, granulocytes are shown in lower, left panel. Increased numbers of dysplastic megakaryocytes (mega), either large with atypically-shaped nuclei (white arrow) or small with hypolobated nuclei (red arrow) are shown in lower right panel. A WT control mouse is shown as a comparison. BM smears were stained with Wright–Giemsa (500x magnification), and BM core biopsies were stained with H&E (200x magnification).



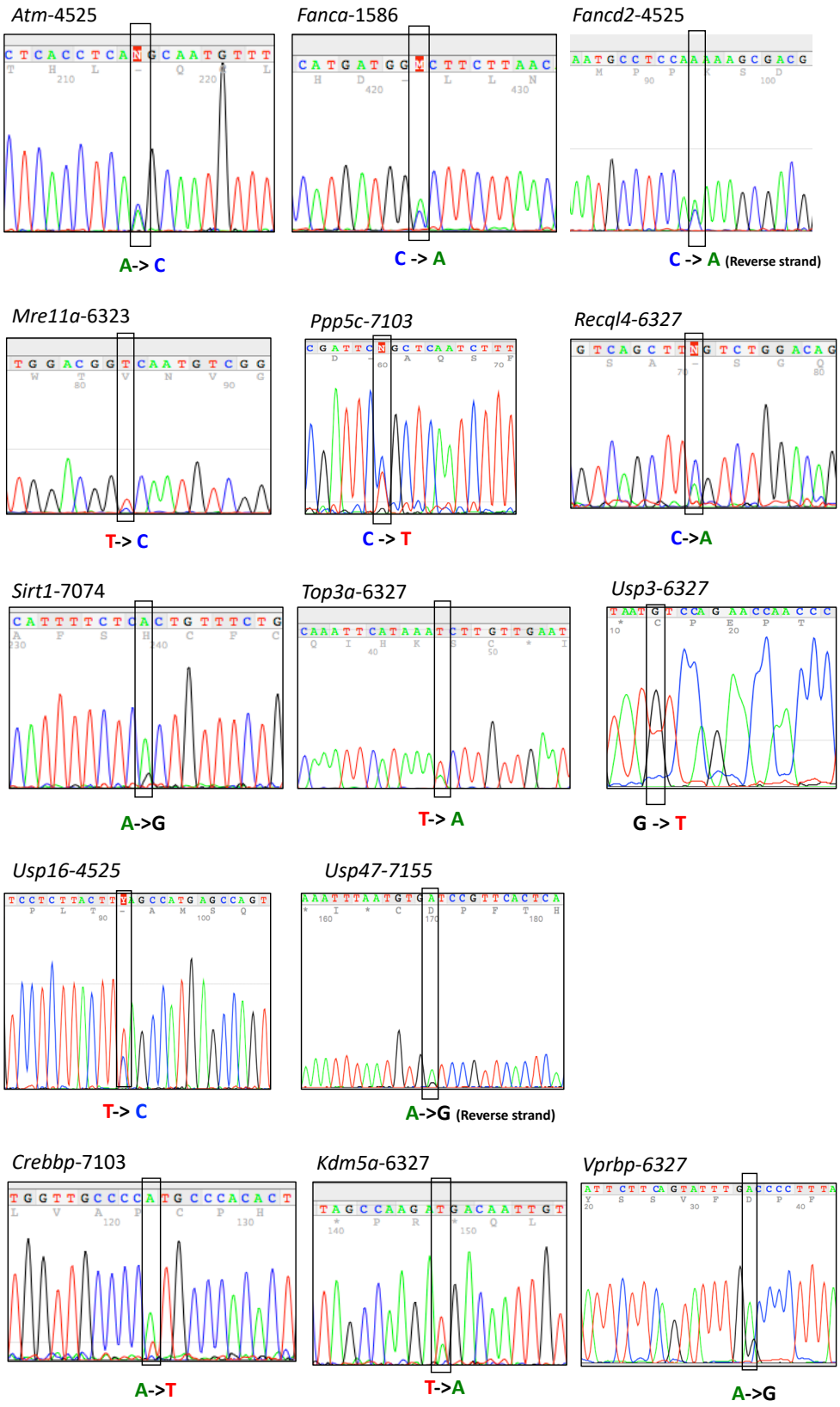
Supplemental Figure 4. DNA repair signatures are downregulated in ENU-exposed *EA-Trp53* LSK samples compared to WT control. LSK$^+$ (Lin-, Sca1$^+$, Kit$^+$) cells were sorted from recipients of *WT*, luc shRNA$^+$ bone marrow (WT control) (n=3) or recipients of *Egr1*$^{+/-}$, *Apc*$^{del/+}$, *Trp53* shRNA+ cells (*EA-Trp53*) treated with ENU (n=3), ~ 70-90 d after transplant, prior to overt leukemia. GSEA, comparing WT control (n=3) to ENU-treated *EA-Trp53* LSK$^+$ (n=3) samples shows that DNA repair signatures are downregulated by loss of *Egr1*, *Apc,* and *Trp53* in LSK cells in ENU-treated conditions. Since DNA repair deficiency has been shown to stimulate ENU-induced mutagenesis (*Cancer Res*. 2003;63(9):2062-2066), this raises the possibility that deregulated DNA repair pathways may collaborate with ENU-mutagenesis to promote malignant transformation.



Supplemental Figure 5. EA-luc mice model features of del(5q) t-MDS. (A) The percent of early erythroblasts in spleen at the time of sacrifice shows massive erythroid expansion in *EA-luc* versus *EA-Trp53*mice consistent with MDS. The corollary is that EA Trp53 mice show increased late erythroblasts. (B) An example of MDS developing in a *EA-luc* mouse is shown. Granulocytic dysplasia (red arrows) is manifested by abnormal nuclear segmentation and chromatin patterns as well as cytoplasmic hypogranulation. Dyserythropoietic features (black arrows) include binucleation and nuclear budding.



Supplemental Figure 6. Development of myeloid disease is slower when only one del(5q) gene, *EGR1*, is haploinsufficient. (A) Kaplan-Meier survival curves of WT recipients transplanted with *Egr1*$^{+/-}$, *Apc*$^{del/+}$ bone marrow cells transduced with *luc* shRNA (*EA-luc*: black) or *Trp53* shRNA (*EA-Trp53*: red), or *Egr1*$^{+/-}$ cells transduced with *Trp53* shRNA (*E-Trp53*: blue). Both donor and recipient mice were treated with ENU. Disease development is significantly slower in *E-Trp53* mice compared to *EA-Trp53* mice (369d vs. 200d, P=0.0177) suggesting that the addition of Apc haploinsufficiency accelerates myeloid disease. **(B)** Histological classification of *E-Trp53* mice shows a trend towards more MDS and less AML compared to *EA-Trp53* mice.



Supplemental Figure 7. Sanger sequencing to validate mutations found by WES. Sanger sequencing of both forward and reverse strands of myeloid neoplasms was performed. The forward strand (unless otherwise noted) with mutated base pair is highlighted with a black box. Key genes involved in the DDR and chromatin modification are shown.

Supplemental Table S1. List of primary MDS and AML mouse samples that were transplanted into secondary recipients

Donor Phenotype*	Donor Tag	Donor phenotype	No. Secondary Recipients	Disease transplantable (no. mice)	Days Disease free	2nd MN§
Egr1$^{+/-}$, Apc$^{del/+}$, Luc shRNA	7075	MDS	5 mice	No	343 d	NA
Egr1$^{+/-}$, Apc$^{del/+}$, Luc shRNA	7073	MDS	5 mice	No	245 d	NA
Egr1$^{+/-}$, Apc$^{del/+}$, Luc shRNA	7068	MDS	5 mice	No	245 d	NA
Egr1$^{+/-}$, Luc shRNA	7022	AML	2 mice	No	244 d	NA
Egr1$^{+/-}$, Apc$^{del/+}$, p53 shRNA	6323	MDS	3 mice	No	244 d	NA
Egr1$^{+/-}$, Apc$^{del/+}$, p53 shRNA	7101	AML	1 mouse	Yes (1/1)	NA	48 d
Egr1$^{+/-}$, Apc$^{del/+}$, p53 shRNA	7103	AML	6 mice	Yes (6/6)	NA	23-26 d
Egr1$^{+/-}$, Apc$^{del/+}$, p53 shRNA	6327	MDS	5 mice	No	365 d	NA
Egr1$^{+/-}$, Apc$^{del/+}$, p53 shRNA	7074	AML	5 mice	Yes (3/5)	390 d	190-329 d

*All donor (phenotype shown) and recipient mice (WT) were ENU treated.
§ Only mice that developed AML were transplantable into secondary recipients.

Supplemental Table 2. Spectral karyotype analysis of MDS and AML samples that underwent whole exome sequencing.

Exome Group §	Tag number	Karyotype [no. cells]*	Clonal Abnormality**
Luc shRNA	7068	40,XX[9]/40,XY[4]/41,XY,+mar[1]	no
Luc shRNA	7155	40,X,+X,der(X)inv(X)(A1B)t(X;13)(F1;A3),del(X)(A2F1),del(4)(D2E2),t(7;18)(E2;E3),-10,der(13)t(X;13)(F1;A3),der(19)t(10;19)(B5;D1)[6]/40,XY[12]	yes
Luc shRNA	7075	40,XY[17]/80,XXYY[1]/40,XX[1]/40,XY,der(5)t(5;5)(A1;E5)[1]	no
Luc shRNA	7134	40,XX[19]/40,XY[1]/39,XX,t(7;10;13;10)(D3;B4;D2;D2),dup(12)(A1B),-19[1]	no
Luc shRNA	7073	40,XY[19]/40,XY,del(12)(A2F2)[1]/34,XY,-7,-8,-11,del(13)(A2C2),-16,-18,-19[1]	no
Luc shRNA	7066	40,XX[2]/40,XY[17]/39,XX,t(4;14)(A1;D3),-17[1]	no
Luc shRNA	7067	40,XX,del(6)(A2D)[2]/40,XY,trp(5)(A1B)[2]/40,XX[8]/40,XY[7]/40,XX,del(3)(A2D)[1]	yes
p53 shRNA	1586†	40,XX,t(7;17)(F1;D)[8]/40,XX,der(2)t(X;2)(D;D)[1]/40,XX[1]	yes
p53 shRNA	4525†	56,XX,+X,+1,+2,del(3)(BF1),+4,+4,+5,+5,+6,+6,del(6)(B3G3),t(6;12)(D;F1),+10,+11,+14,+15,+16,+17,+19[7]/58,idem,+14,+15[1]/40,XX[3]/40,XY[1]	yes
p53 shRNA	7914‡	40,XY[21]	no
p53 shRNA	6323	39,XY,-13[4]/40,XY[16]	yes
p53 shRNA	6327	40,XY[2]/40,XX[4]/39,X,-X or 39,X,-Y[4]/41,XX,+8[1]/42,XX,+2,+4,+8,-16,-18,+mar[1]/37,X,-X,-11,del(13)(A5D2),-17 or 37,X,-Y,-11,del(13)(A5D2),-17[1]	yes
p53 shRNA	7074	40,XX[5]/40,XY[9]	no
p53 shRNA	7101	59,X,der(X)t(X;5)(A2;B),+1,+2,+3,+4,+6,+der(7)t(7;15)(B5;C),+9,+der(10)t(3;10)(F1;C1),+11,+11,+12,+14,+14,del(14)(D2E2),+15,+16,+17,+18,+19,+mar[6]/59,idem,del(16)(B1B3)[4]/58,idem,t(3;5)(G;E5),-der(10) t(3;10),del(16)(B1B3)[3]/60,idem,+9,der(9)t(4;9)(C4;F1)[1]/57,idem,t(2;3)(H1;H1),der(3)t(2;3)(H1;H1),-der(10)t(3;10),der(10)t(5;10)(F;E3),-19[1]/56,idem,-3,+der(4)t(4;11)(C4;B5),-6,-der(10)t(3;10),+der(10)t(5;10)(F;E3),-15,-19[1]/57,idem,dic(X;15)(A1;A1)der(X)t(X;5),-3,-9,+10,-11,-15,+17,+18,del(18)(CE3),der(18)t(15;18)(C;D)[1]/56,idem,+der dic(2;8)(A1;A1)del(8)(A2E1),-3,+10,-11,-11,-del(14)(D2E2),-17[1]/55,idem,+der(X)t(X;15)(C;C),-3,-9,t(9;18)(F1;D),-der(10)t(3;10),+10,-11,der(11)t(8;11)(C3;D),-15,-mar[1]/40,XY[1]	yes
p53 shRNA	7103	41,XY,+1[15]/40,XX,t(2;16)(E2;B5),+5,del(5)(E3F),-6[2]/40,XY[3]	yes

§ Donor mice were *Egr1*$^{+/-}$, *Apc*$^{del/+}$ and recipient mice were WT (C57Bl/6). shRNA used to transduce bone marrow cells is shown. Both donor and recipient mice were ENU-treated; exceptions are listed († and ‡).
*A minimum of 10 metaphase cells were analyzed.
**2/7 (29%) Luc-shRNA and 6/8 (75%) p53-shRNA mice had a clonal karyotypic abnormality.
† Donor and recipient mice were not ENU treated.
‡ Only the recipient mouse was ENU treated.

Supplemental Table 3. List of mutations identified by whole exome sequencing analysis in bone marrow isolated from *EA-Luc* MDS and *EA-Trp53* AML samples.

Mouse Tag	Mutation Type	UCSC mm9	Chromosome	Reference	Mutation	Gene	NCBI Reference	Transcript position	Amino acid position	GERP Score	Amino acid change	Expressed in MN (SRA061655)
7068-luc	missense	107244898	chr9	T	C	*6430571L13Rik*	NM_175486	617	73	3.35	V73A	No
7068-luc	missense	111506097	chr7	A	C	*A530023O14Rik*	NM_175648	585	22	2.45	L22R	No
7068-luc	missense	76658499	chr5	A	T	*Clock*	NM_007715	2364	659	2.37	N659K	Yes
7068-luc	missense	62990910	chr4	A	T	*Col27a1*	NM_025685	5555	1714	3.6	Q1714L	Yes
7068-luc	missense	120868629	chr9	C	G	*Ctnnb1*	NM_007614	2552	780	3.92	D780E	Yes
7068-luc	missense	105934937	chr12	A	G	*Dicer1*	NM_148948	4872	1532	3.97	Y1532H	Yes
7068-luc	missense	63773233	chr16	C	A	*Epha3*	NM_010140	426	106	3.01	C106F	Yes
7068-luc	missense	118363937	chr14	A	T	*Gpc6*	NM_001079844	1957	446	3.52	M446L	Yes
7068-luc	missense	135509836	chr4	T	G	*Hmgcl*	NM_008254	345	106	3.69	L106R	Yes
7068-luc	missense	80129331	chr9	T	C	*Myo6*	NM_001039546	2356	714	3.87	L714P	Yes
7068-luc	missense	13490804	chr12	T	A	*Nbas*	NM_027706	5657	1878	3.55	I1878N	Yes
7068-luc	missense	97103330	chr11	T	A	*Npepps*	NM_008942	1001	295	3.97	D295V	Yes
7068-luc	missense	49325855	chr8	G	A	*Odz3*	NM_011857	5441	1798	2.51	T1798I	Yes
7068-luc	missense	115959430	chr4	T	C	*Pik3r3*	NM_181585	1161	256	3.46	I256T	Yes
7068-luc	missense	108762980	chr9	T	A	*Slc26a6*	NM_134420	2419	527	3.17	L527Q	Yes
7068-luc	missense	14321856	chr2	A	T	*Slc39a12*	NM_001012305	809	211	2.81	I211F	Yes
7068-luc	missense	42175010	chr9	C	A	*Tecta*	NM_009347	3550	1095	3.85	R1095L	Yes
7068-luc	missense	45140621	chr9	C	T	*Tmprss13*	NM_001013373	606	191	3.6	R191C	Yes
7068-luc	missense	37556701	chr7	C	A	*Tshz3*	NM_172298	3227	1032	3.85	S1032Y	Yes
7068-luc	missense	20608472	chr17	A	T	*Vmn2r108*	NM_001104570	751	251	2.17	I251N	No
7068-luc	nonsense	66797755	chrX	C	T	*Aff2*	NM_008032	813	118	NA	Q118*	Yes
7068-luc	nonsense	120268270	chr14	G	A	*Hs6st3*	NM_015820	1017	289	NA	W289*	Yes
7068-luc	nonsense	31135122	chr17	C	T	*Umodl1*	NM_177465	3447	1128	NA	Q1128*	Yes
7068-luc	nonsense	109481186	chr5	A	T	Vmn2r11	NM_001104622	1418	473	NA	Y473*	No
7155-luc	missense	83133776	chrX	A	C	*5430427O19Rik*	NM_001163539	773	203	2.8	K203T	No
7155-luc	missense	69162014	chr2	A	T	*Abcb11*	NM_021022	390	88	2.49	D88E	Yes
7155-luc	missense	56797067	chr19	T	G	*Adrb1*	NM_007419	206	69	2.79	V69G	Yes
7155-luc	missense	58433499	chr16	T	G	*Dcbld2*	NM_028523	706	162	3.47	V162G	Yes
7155-luc	missense	60536895	chr11	A	G	*Flii*	NM_022009	330	100	3.7	I100T	Yes
7155-luc	missense	108146876	chr5	G	C	*Gfi1*	NM_010278	1660	386	3.73	P386A	Yes
7155-luc	missense	118005354	chr5	T	A	*Ksr2*	NM_001034873	1686	286	2.49	L286Q	Yes
7155-luc	missense	68909449	chr2	T	C	*Lass6*	NM_172856	878	267	3.94	F267L	Yes
7155-luc	missense	193584028	chr1	T	C	*Lpgat1*	NM_172266	838	210	3.97	V210A	Yes
7155-luc	missense	75008277	chr9	C	A	*Myo5a*	NM_010864	2232	602	3.48	T602N	Yes
7155-luc	missense	25335364	chr3	T	A	*Nlgn1*	NM_138666	2420	374	3.72	I374L	Yes
7155-luc	missense	119196810	chr7	T	C	*Usp47*	NM_133758	321	40	3.48	I40T	Yes
7134-luc	missense	109002644	chr9	T	C	*Plxnb1*	NM_172775	322	18	2.13	V18A	Yes
7073-luc	missense	53746221	chrX	T	G	*Ddx26b*	NM_172779	1527	400	3.31	L400V	Yes
7073-luc	missense	113750443	chr13	A	G	*Dhx29*	NM_172594	2978	993	3.74	Y993C	Yes
7073-luc	missense	34285625	chr1	T	A	*Dst*	NM_134448	15302	5101	3.94	L5101H	Yes
7073-luc	missense	88988568	chr3	T	C	*Fam189b*	NM_001014995	909	137	2.29	V137A	Yes
7073-luc	missense	44149507	chr5	A	T	*Fbxl5*	NM_178729	1901	601	3.69	F601I	Yes
7073-luc	missense	126689230	chr6	A	C	*Kcna6*	NM_013568	1462	238	3.01	I238S	Yes
7073-luc	missense	6382003	chr7	T	C	*LOC100042450*	NM_001134752	396	78	2.24	W78R	No
7073-luc	missense	69305107	chr2	T	A	*Lrp2*	NM_001081088	9739	3189	4.07	D3189V	Yes
7073-luc	missense	60202473	chr12	T	A	*Mia2*	NM_177321	131	44	2.24	V44D	Yes
7073-luc	missense	68552848	chrX	T	A	*Mtm1*	NM_019926	1233	387	2.19	S387T	Yes
7073-luc	missense	75143932	chr9	T	C	*Myo5c*	NM_001081322	4637	1501	3.86	I1501T	Yes
7073-luc	missense	179992347	chr2	C	G	*Rps21*	NM_025587	91	3	2.9	N3K	Yes
7073-luc	missense	117177913	chr10	A	G	*Slc35e3*	NM_029875	739	190	3.94	Y190H	Yes
7073-luc	missense	8049996	chr10	A	G	*Ust*	NM_177387	745	107	3.62	V107A	Yes
7073-luc	missense	18940660	chr8	A	G	*Xkr5*	NM_001113350	629	197	2.95	L197P	Yes
7073-luc	missense	46388601	chr17	C	G	*Yipf3*	NM_145353	1150	328	3.67	L328V	Yes
7066-luc	missense	35262026	chr9	A	T	*Cdon*	NM_021339	514	162	2.6	H162L	Yes
7066-luc	missense	12887711	chr10	T	A	*Fam164b*	NM_029172	282	82	3.64	Q82L	Yes
7066-luc	missense	154534063	chr4	A	T	*Ski*	NM_011385	1227	405	3.51	Y405N	Yes
7066-luc	missense	4265629	chr19	T	C	*Ssh3*	NM_198113	948	286	2.79	D286G	Yes
7066-luc	missense	5752992	chr17	C	G	*Zdhhc14*	NM_146073	2216	457	3.01	P457A	Yes
7066-luc	nonsense	76334802	chr15	G	A	*Dgat1*	NM_010046	508	158	NA	Q158*	Yes
7066-luc	nonsense	61596851	chr10	T	A	*Neurog3*	NM_009719	880	214	NA	L214*	Yes
7067-luc	missense	99432100	chr15	G	T	*Aqp6*	NM_175087	270	88	3.63	V88L	Yes
7067-luc	missense	97459014	chr8	T	A	*Gpr114*	NM_001033468	564	161	3.13	V161E	Yes
7067-luc	missense	166425568	chrX	G	A	*Mid1*	NM_010797	1746	522	3.63	D522N	Yes
7067-luc	missense	35177749	chr6	A	G	*Nup205*	NM_027513	4332	1439	3.59	D1439G	Yes
7067-luc	missense	170115152	chr1	T	C	*Pbx1*	NM_183355	1798	349	2.63	S349G	Yes
7067-luc	missense	59757737	chr10	T	G	*Psap*	NM_011179	713	200	3.74	C200G	Yes
7067-luc	missense	105500806	chr7	A	G	*Tsku*	NM_001024619	881	276	3.22	F276S	Yes
7067-luc	missense	166881631	chr2	A	C	*Znfx1*	NM_001033196	1427	291	3.94	V291G	Yes
1586-p53	missense	125820249	chr8	C	A	*Fanca*	NM_016925	1670	550	3.01	A550S	Yes
1586-p53	missense	25547154	chr4	A	G	*Fut9*	NM_010243	1315	269	3.74	V269A	Yes
1586-p53	missense	94385174	chr15	A	G	*Irak4*	NM_029926	662	183	3.52	Q183R	Yes
1586-p53	missense	45704170	chr17	G	A	*Slc35b2*	NM_028662	1690	376	2.65	E376K	Yes
1586-p53	nonsense	132341136	chr4	G	A	*BC013712*	NM_001033308	1703	565	NA	Q565*	No
1586-p53	indel	87247594	chr3	GTTC	G	*Fcrl5*	NM_001113238	327	NA	NA	deletion	Yes
1586-p53	indel	37024741	chr3	A	AGCTTGAAGTGGG	*Il2*	NM_008366	134	NA	NA	insertion	No
1586-p53	indel	41545949	chr3	AT	A	*Sclt1*	NM_001081411	487	NA	NA	deletion	Yes

4525-p53	missense	7217906	chr18	C	T	*Armc4*	NM_001081393	1946	602	3.59	R602Q	Yes
4525-p53	missense	53307231	chr9	A	C	*Atm*	NM_007499	3293	1052	3.77	L1052R	Yes
4525-p53	missense	85205829	chr15	G	A	*Atxn10*	NM_016843	553	157	3.51	A157T	Yes
4525-p53	missense	113537391	chr6	G	T	*Fancd2*	NM_001033244	3996	1300	3.66	V1300L	Yes
4525-p53	missense	125141176	chr2	G	A	*Fbn1*	NM_007993	7207	2308	3.82	R2308C	Yes
4525-p53	missense	56921699	chr12	T	C	*Garnl1*	NM_001003719	455	19	3.18	D19G	Yes
4525-p53	missense	44351292	chr15	T	C	*Pkhd1l1*	NM_138674	3400	1134	3.87	S1134P	Yes
4525-p53	missense	11079811	chr1	G	A	*Prex2*	NM_029525	861	178	4.07	R178Q	Yes
4525-p53	missense	34089002	chr17	A	G	*Rps18*	NM_011296	465	149	2.69	S149P	Yes
4525-p53	missense	74672377	chr11	C	T	*Sgsm2*	NM_197943	1691	498	3.63	R498Q	Yes
4525-p53	missense	31829984	chr5	C	T	*Slc4a1ap*	NM_009206	617	197	2.77	P197L	Yes
4525-p53	missense	87472000	chr16	T	C	*Usp16*	NM_024258	932	258	2.71	L258S	Yes
4525-p53	missense	115773823	chr7	A	C	*Olfr508*	NM_146773	316	106	2.31	T106P	No
4525-p53	missense	115811700	chr7	A	G	*Olfr510*	NM_146311	769	257	2.59	T257A	No
4525-p53	missense	38823883	chr19	T	C	Plce1	NM_019588	4902	1614	2.23	S1614P	Yes
4525-p53	nonsense	112078884	chr14	C	A	*Slitrk5*	NM_198865	1334	239	NA	C239*	Yes
4525-p53	indel	31236148	chr5	T	TTTC	*Cgref1*	NM_001160149	614	NA	NA	insertion	Yes
4525-p53	indel	57596182	chr6	T	TTGATGCA GAGGG	*Herc5*	NM_025992	1820	NA	NA	insertion	Yes
4525-p53	indel	19141505	chr8	A	AC	*Spag11b*	NM_001034905	235	NA	NA	insertion	No
7914-p53	missense	120266615	chr13	C	A	4833420G17Rik	NM_001113550	1905	484	3.81	T484K	No
7914-p53	missense	110149834	chr9	C	T	Cspg5	NM_013884	1280	378	3.17	P378L	Yes
7914-p53	missense	76024552	chr11	G	C	Gemin4	NM_177367	2908	962	3.84	P962A	Yes
7914-p53	missense	69864651	chr9	C	T	Gtf2a2	NM_001039519	257	33	3.85	A33V	Yes
7914-p53	missense	52853453	chr18	G	T	Gykl1	NM_010293	110	26	2.54	L26F	No
7914-p53	missense	65217552	chr1	C	T	*Idh1*	NM_010497	563	132	2.55	R132Q	Yes
7914-p53	missense	78353536	chr11	G	A	Ift20	NM_018854	574	68	3.67	E68K	Yes
7914-p53	missense	105227801	chr7	C	T	Myo7a	NM_008663	2766	836	3.77	R836H	Yes
7914-p53	missense	86603220	chr7	G	A	Polg	NM_017462	2095	578	3.17	R578W	Yes
7914-p53	missense	20594442	chr16	C	T	Vwa5b2	NM_182636	988	167	2.91	S167F	Yes
7914-p53	nonsense	4309343	chr9	C	A	Aasdhppt	NM_026276	151	32	NA	E32*	Yes
7914-p53	nonsense	85780699	chr6	G	A	*Cml4*	NM_023455	613	149	NA	R149*	Yes
7914-p53	nonsense	42198073	chr10	C	T	Lace1	NM_145743	298	45	NA	W45*	Yes
6323-p53	missense	45653867	chr17	A	T	*Aars2*	NM_198608	1675	554	3.59	L554F	Yes
6323-p53	missense	10509326	chr18	C	T	AK220484	NM_001083628	1860	547	3.18	H547Y	No
6323-p53	missense	31370522	chr5	T	C	*Cad*	NM_023525	3080	979	3.49	V979A	Yes
6323-p53	missense	80186792	chr2	T	C	Dnajc10	NM_024181	2420	645	2.23	Y645H	Yes
6323-p53	missense	106268515	chr11	A	T	*Ern1*	NM_023913	2212	698	3.32	M698K	Yes
6323-p53	missense	80665688	chr3	A	T	*Glrb*	NM_010298	683	183	3.48	C183S	Yes
6323-p53	missense	83993227	chrX	A	T	*Il1rapl1*	NM_001160403	2092	482	4.07	V482E	Yes
6323-p53	missense	99877454	chr11	T	A	*Krt33a*	NM_027983	72	3	3.79	Y3F	Yes
6323-p53	missense	14601550	chr9	T	C	*Mre11a*	NM_018736	595	156	3.49	S156P	Yes
6323-p53	missense	47439140	chr19	C	A	*Sh3pxd2a*	NM_008018	646	124	3.14	R124L	Yes
6323-p53	missense	37291145	chr16	T	G	*Stxbp5l*	NM_001114611	628	158	3.50	T158P	Yes
6323-p53	missense	104343017	chr12	A	C	*Unc79*	NM_001081017	3422	1141	3.85	Y1141S	No
6327-p53	missense	54818172	chr11	C	T	*Anxa6*	NM_013472	871	245	3.23	V245M	Yes
6327-p53	missense	94710459	chr13	G	A	*Arsb*	NM_009712	1477	460	2.54	V460I	Yes
6327-p53	missense	29718539	chr14	T	A	*Cacna2d3*	NM_009785	3284	1063	3.37	N1063I	Yes
6327-p53	missense	18096848	chr9	T	G	Chordc1	NM_025844	138	3	2.46	L3R	Yes
6327-p53	missense	40238859	chr19	T	C	Cyp2c70	NM_145499	949	314	2.33	K314R	No
6327-p53	missense	138193490	chr7	T	A	*Dmbt1*	NM_007769	611	201	3.08	I201N	Yes
6327-p53	missense	118602238	chr3	G	A	*Dpyd*	NM_170778	1210	371	4.07	R371Q	Yes
6327-p53	missense	108778831	chr6	T	A	*Edem1*	NM_138677	197	33	2.83	F33Y	Yes
6327-p53	missense	75733955	chr15	A	G	Eef1d	NM_029663	394	95	2.15	I95T	Yes
6327-p53	missense	125027119	chr5	A	C	*Eif2b1*	NM_145371	201	53	3.44	I53R	Yes
6327-p53	missense	34039906	chr18	G	T	*Epb4.1l4a*	NM_013512	1144	123	2.66	A123D	Yes
6327-p53	missense	55096159	chr11	T	C	*Fat2*	NM_001029988	7239	2410	3.87	D2410G	Yes
6327-p53	missense	29400619	chr6	T	C	*Flnc*	NM_001081185	4651	1449	3.72	C1449R	Yes
6327-p53	missense	88862329	chr17	T	A	*Foxn2*	NM_180974	450	88	3.49	I88K	Yes
6327-p53	missense	97198660	chr5	G	A	*Fras1*	NM_175473	11377	3507	3.55	V3507I	Yes
6327-p53	missense	64677254	chr7	C	A	*Gabra5*	NM_176942	926	195	3.32	A195S	No
6327-p53	missense	151757128	chr3	T	A	*Gipc2*	NM_016867	940	310	3.67	M310L	Yes
6327-p53	missense	7110048	chr11	A	G	*Igfbp3*	NM_008343	739	203	2.82	S203P	Yes
6327-p53	missense	174426320	chr1	C	T	*Igsf9*	NM_033608	2510	730	3.21	L730F	Yes
6327-p53	missense	62599390	chr9	A	G	*Itga11*	NM_176922	1300	404	3.39	I404V	Yes
6327-p53	missense	120376908	chr6	T	A	*Kdm5a*	NM_145997	3970	1152	3.71	M1152K	Yes
6327-p53	missense	75106684	chr18	T	A	*Lipg*	NM_010720	1421	378	3.86	D378V	Yes
6327-p53	missense	39703629	chr15	G	A	*Lrp12*	NM_172814	2583	837	3.56	P837S	Yes
6327-p53	missense	148867371	chr4	A	G	*Lzic*	NM_026963	1075	134	3.72	I134V	Yes
6327-p53	missense	12305154	chrX	A	T	*Med14*	NM_001048208	1688	472	3.7	M472K	Yes
6327-p53	missense	30697028	chr5	A	C	*Otof*	NM_031875	1077	315	3.94	I315S	Yes
6327-p53	missense	37090068	chr18	A	T	Pcdha1	NM_054072	130	44	2.33	T44S	Yes
6327-p53	missense	36731351	chr9	T	C	*Pknox2*	NM_148950	571	136	3.67	K136E	Yes
6327-p53	missense	128935939	chr2	T	A	*Polr1b*	NM_009086	1241	384	4.07	F384I	Yes
6327-p53	missense	4438003	chr7	T	C	*Ppp1r12c*	NM_029834	1001	307	2.93	D307G	Yes
6327-p53	missense	77996371	chr11	C	T	*Rpl23a*	NM_207523	183	48	3.65	R48Q	Yes
6327-p53	missense	124831547	chr5	G	A	*Sbno1*	NM_001081203	3662	1199	3.49	P1199S	Yes
6327-p53	missense	32132707	chr12	A	G	*Slc26a3*	NM_021353	374	82	4.07	S82G	No
6327-p53	missense	61524484	chrX	A	G	*Slitrk4*	NM_178740	2069	584	3.63	L584S	Yes
6327-p53	missense	60576900	chr11	T	A	*Top3a*	NM_009410	471	70	3.2	I70F	Yes
6327-p53	missense	36570305	chr3	T	G	*Trpc3*	NM_019510	630	148	3.64	H148P	Yes
6327-p53	missense	66366372	chr9	G	T	*Usp3*	NM_144937	1516	471	4.07	H471N	Yes
6327-p53	missense	106741016	chr9	A	G	*Vprbp*	NM_001015507	1124	334	3.61	T334A	Yes
6327-p53	nonsense	76539876	chr15	C	A	*Recql4*	NM_058214	462	155	NA	E155*	Yes

6327-p53	indel	88931096	chr5	CCAAATAAA CCCTTTGTG	C	*Enam*	NM_017468	1512	NA	NA	deletion	Yes
7074-p53	missense	126877946	chr2	T	G	*Ap4e1*	NM_175550	1922	627	3.1	F627V	Yes
7074-p53	missense	91510163	chr7	A	T	*Arnt2*	NM_007488	120	16	3.17	I16K	Yes
7074-p53	missense	87437591	chr16	G	A	*Rwdd2b*	NM_016924	324	52	3.36	S52L	Yes
7074-p53	missense	106495865	chr7	T	C	*Serpinh1*	NM_001111043	902	210	3.08	D210G	Yes
7074-p53	missense	62784553	chr10	A	G	*Sirt1*	NM_001159590	1370	449	4.07	V449A	Yes
7101-p53	missense	26939601	chr2	G	T	*Adamtsl2*	NM_029981	589	132	3.68	W132L	Yes
7103-p53	missense	52161233	chr7	A	G	*Ap2a1*	NM_001077264	1420	426	3.44	L426P	Yes
7103-p53	missense	108014203	chr9	C	T	*Bsn*	NM_007567	6804	2227	2.56	G2227D	Yes
7103-p53	missense	26207929	chr2	T	C	Card9	NM_001037747	1513	505	2.12	K505R	Yes
7103-p53	missense	106662845	chr11	T	C	*Ccdc45*	NM_177088	620	179	2.93	I179T	Yes
7103-p53	missense	84742712	chr4	T	C	*Cntln*	NM_175275	3473	1112	3.1	L1112P	Yes
7103-p53	missense	4119067	chr16	A	T	*Crebbp*	NM_001025432	2615	812	3.79	M812K	Yes
7103-p53	missense	86457453	chr4	T	G	*Dennd4c*	NM_001081014	2762	796	3.94	V796G	Yes
7103-p53	missense	83862513	chr11	C	A	*Dusp14*	NM_019819	476	68	3.86	W68L	Yes
7103-p53	missense	55213774	chr6	G	A	*Fam188b*	NM_177883	1446	441	3.11	G441D	No
7103-p53	missense	151172132	chr5	A	T	*Fry*	NM_172887	1607	423	3.84	N423I	Yes
7103-p53	missense	18250667	chr1	A	T	Gm15386	NM_001040027	135	46	2.48	C46S	No
7103-p53	missense	80965692	chr10	G	T	Gna15	NM_010304	1327	353	2.06	R353S	Yes
7103-p53	missense	28169151	chr5	T	A	Htr5a	NM_008314	665	55	2.07	F55I	No
7103-p53	missense	68102320	chr17	C	T	*Lama1*	NM_008480	2133	688	4.07	A688V	Yes
7103-p53	missense	86585576	chr3	G	T	*Lrba*	NM_030695	8843	2853	3.7	R2853L	Yes
7103-p53	missense	86350775	chr3	T	C	*Mab21l2*	NM_011839	1430	280	3.46	Y280C	Yes
7103-p53	missense	119481461	chr2	A	T	*Ndufaf1*	NM_027175	1176	304	3.33	I304N	Yes
7103-p53	missense	37120185	chr18	T	C	*Pcdha5*	NM_009959	92	31	2.91	L31P	Yes
7103-p53	missense	75563943	chr5	T	G	*Pdgfra*	NM_001083316	906	237	3.48	V237G	Yes
7103-p53	missense	17592279	chr7	C	T	*Ppp5c*	NM_011155	1212	371	2.75	R371Q	Yes
7103-p53	missense	154433543	chr1	A	T	*Rgl1*	NM_016846	441	114	3.82	L114Q	Yes
7103-p53	missense	46892636	chr1	A	T	*Slc39a10*	NM_172653	399	117	2.86	V117E	Yes
7103-p53	missense	163681114	chrX	C	T	*Tlr8*	NM_133212	2707	891	3.65	E891K	Yes
7103-p53	missense	119441922	chr14	T	A	*Uggt2*	NM_001081252	2457	789	3.86	T789S	No
7103-p53	missense	87904065	chr5	T	A	*Ugt2a2*	NM_001024148	117	23	3.87	N23I	No
7103-p53	missense	121101861	chr9	G	T	*Ulk4*	NM_177589	2059	634	2.61	T634K	Yes
7103-p53	missense	53099816	chr19	A	T	*Xpnpep1*	NM_133216	175	17	3.38	M17K	Yes
7103-p53	splice junction	132121268	chr2	T	C	Cds2	NM_138651	477	NA	3.17	NA	Yes

Supplemental Table 4. Pathogenic prediction algorithm scores to predict deleterious mutations.

Mouse Tag	Gene	Amino acid change	Mutation Type	GERP[1]	SIFT[2]	PolyPhen[3]	Clin Var[4]
7103-p53	Crebbp	M812K	missense	3.79	deleterious (0)	possibly damaging (0.627)	none
6327-p53	Kdm5a	M1152K	missense	3.71	tolerated (0.07)	benign (0.119)	none
6327-p53	Vprbp	T334A	missense	3.61	deleterious (0.01)	probably damaging (0.969)	none
7914-p53	Idh1	R132Q		2.55	deleterious low confidence (0)	NA	NM_005896.3(IDH1):c.395G>T (p.Arg132Leu) NM_005896.3(IDH1):c.395G>C (p.Arg132Pro) NM_005896.3(IDH1):c.394C>A (p.Arg132Ser) NM_005896.3(IDH1):c.395G>A (p.Arg132His) NM_005896.3(IDH1):c.394C>G (p.Arg132Gly) NM_005896.3(IDH1):c.394C>T (p.Arg132Cys)
4525-p53	Atm	L1052R	missense	3.77	deleterious (0)	probably damaging (0.935)	NM_000051.3(ATM):c.3149T>G (p.Leu1050Arg)
1586-p53	Fanca	A550S	missense	3.01	deleterious (0)	probably damaging (0.996)	none
4525-p53	Fancd2	V1300L	missense	3.66	tolerated (0.25)	benign (0.23)	none
6323-p53	Mre11a	S156P	missense	3.49	deleterious (0.03)	benign (0.077)	none
7103-p53	Ppp5c	R371Q	missense	2.75	deleterious (0)	probably damaging (1)	none
6327-p53	Recql4	E155*	nonsense	NA	NA	NA	none
7074-p53	Sirt1	V449A	missense	4.07	tolerated (0.28)	benign (0.05)	none
6327-p53	Top3a	I70F	missense	3.2	deleterious (0)	probably damaging (0.984)	none
6327-p53	Usp3	H471N	missense	4.07	deleterious (0)	probably damaging (0.984)	none
6327-p53	Rpl23a	R48Q	missense	3.65	tolerated (0.25)	benign (0.052)	none
4525-p53	Rps18	S149P	missense	2.69	deleterious (0.04)	benign (0.307)	none
4525-p53	Fbn1	R2308C	missense	3.82	deleterious (0)	probably damaging (0.938)	none
1586-p53	Fcrl5	deletion	indel	NA	NA	NA	none
4525-p53	Herc5	insertion	indel	NA	NA	NA	none
6327-p53	Igfbp3	S203P	missense	2.82	tolerated (0.23)	possibly damaging (0.885)	none
1586-p53	Irak4	Q183R	missense	3.52	tolerated (1)	NA	none
7103-p53	Lrba	R2853L	missense	3.7	deleterious (0)	probably damaging (0.995)	NM_001364905.1(LRBA):c.8551C>T (p.Arg2851Cys)
7103-p53	Pdgfra	V237G	missense	3.48	deleterious (0)		NM_006206.6(PDGFRA):c.670G>C (p.Val224Leu) NM_006206.6(PDGFRA):c.670G>A (p.Val224Met)
7103-p53	Rgl1	L114Q	missense	3.82	deleterious (0)	probably damaging (0.999)	none
7103-p53	Tlr8	E891K	missense	3.65	deleterious (0)	possibly damaging (0.859)	none
6327-p53	Pknox2	K136E	missense	3.67	deleterious (0.03)	possibly damaging (0.902)	none
7103-p53	Xpnpep1	M17K	missense	3.38	deleterious (0)	probably damaging (1)	none
7067-luc	Chd1	N555K	missense	2.40	deleterious (0)	probably damaging (0.996)	none
7155-luc	Usp47	I40T	missense	3.48	tolerated (0.34)	benign (0.01)	none
7073-luc	Rps21	N3K	missense	2.9	deleterious (0.04)	NA	none
7073-luc	Mtm1	S387T	missense	2.19	deleterious (0.01)	benign (0.129)	NM_000252.2(MTM1):c.1160C>A (p.Ser387Tyr)
7068-luc	Pik3r3	I256T	missense	3.46	deleterious (0)	possibly damaging (0.792)	none
7068-luc	Aff2	Q118*	nonsense	NA	NA	NA	none
7068-luc	Ctnnb1	D780E	missense	3.92	deleterious (0.01)	possibly damaging (0.777)	none
7068-luc	Dicer1	Y1532H	missense	3.97	deleterious (0)	probably damaging (0.999)	NM_177438.2(DICER1):c.4638C>A (p.Tyr1546Ter) NM_177438.2(DICER1):c.4637dup (p.Tyr1546Ter)
7155-luc	Gfi1	I385M	missense	3.73	deleterious (0)	probably damaging (0.972)	none
7067-luc	Pbx1	S349G	missense	2.63	tolerated (0.98)	benign (0)	none
7066-luc	Ski	Y405N	missense	3.51	deleterious (0.01)	NA	none
7067-luc	Znfx1	V291G	missense	3.94	deleterious (0)	probably damaging (0.917)	none

[1]Only missense mutations with a GERP score of <2.0 were considered for further evaluation.
[2]The SIFT score ranges from 0.0 (deleterious) to 1.0 (tolerated).
[3]The Polyphen score ranges from 0.15 (benign) to 1.0 (damaging).
[4]ClinVar was used to identify mutations resulting in the identical amino acid shift in humans.

Supplemental Table 5. Top Ten Gene Ontology (GO) biological process gene sets that overlap with mutated genes identified by WES.

GO Gene Set Name	# Genes in Gene Set (K)	# Genes in Overlap (k)	k/K	p-value	FDR q-value	Gene names*
CHROMOSOME_ ORGANIZATION	1207	15	0.0124	5.44E-14	4.00E-10	SIRT1, ATM, CTNNB1, DCAF1, USP3, FANCD2, MRE11, RECQL4, TOP3A, GFI1, CREBBP, KDM5A, SKI, CHD1, ZNFX1
DNA_METABOLIC_ PROCESS	850	12	0.0141	7.44E-12	2.41E-08	SIRT1, ATM, CTNNB1, DCAF1, USP3, FANCD2, MRE11, RECQL4, TOP3A, FANCA, USP47, PPP5C
COVALENT_CHROMATIN_ MODIFICATION	467	10	0.0214	9.82E-12	2.41E-08	SIRT1, ATM, CTNNB1, DCAF1, USP3, GFI1, CREBBP, KDM5A, SKI, CHD1
IMMUNE_SYSTEM_ DEVELOPMENT	972	12	0.0123	3.50E-11	6.44E-08	SIRT1, ATM, CTNNB1, DCAF1, GFI1, CREBBP, FANCD2, FANCA, PBX1, PDGFRA, FBN1, HERC6
CHROMATIN_ ORGANIZATION	792	11	0.0139	7.84E-11	1.15E-07	SIRT1, ATM, CTNNB1, DCAF1, GFI1, CREBBP, USP3, KDM5A, SKI, CHD1, ZNFX1
DNA_REPAIR	544	9	0.0165	1.18E-09	1.45E-06	SIRT1, ATM, USP3, FANCD2, FANCA, MRE11, RECQL4, USP47, PPP5C
REGULATION_OF_ HISTONE_MODIFICATION	140	6	0.0429	3.31E-09	3.47E-06	SIRT1, ATM, CTNNB1, GFI1, KDM5A, SKI
CELL_CYCLE	1847	13	0.007	4.30E-09	3.69E-06	SIRT1, ATM, CTNNB1, GFI1, USP3, FANCD2, FANCA, MRE11, RECQL4, USP47, PPP5C, PBX1, TOP3A
SEX_DIFFERENTIATION	268	7	0.0261	4.51E-09	3.69E-06	SIRT1, CTNNB1, FANCA, PBX1, KDM5A, PDGFRA, IDH1
INTERSPECIES_INTERACTION_BETWEEN_ ORGANISMS	927	10	0.0108	7.41E-09	5.45E-06	SIRT1, CTNNB1, PDGFRA, GFI1, MRE11, DCAF1, CREBBP, CHD1, RPL23A, RPS21

* *TOP3A* gene is in DNA Double Strand Break Repair Super Path (Gene Cards Suite, Pathway Unification Database)

* IDH1 mutations have been linked to altered DNA repair (Cancer Cell 2016;30(2):337-48)

Supplemental Table 6. Number of mutated samples in each histology subtype curated by the Catalogue of Somatic Mutations in Cancer (COSMIC) database.

Gene	Hematological Neoplasms*	AML*	t-MN*
IDH1	1285/33889 (3.79)	1068/17717 (6.03)	15/282 (5.32)
ATM	478/8077 (5.92)	4/1230 (0.33)	1/82 (1.21)
FANCA	11/4443 (0.25)	1/934 (0.11)	0/43 (0)
FANCD2	10/4239 (0.24)	0/933 (0)	0/43 (0)
MRE11	5/4376 (0.11)	1/934 (0.11)	0/43 (0)
PPP5C	1/4168 (0.02)	0/933 (0)	0/42 (0)
RECQL4	16/4375 (0.37)	13/934 (1.39)	0/43 (0)
SIRT1	0/4168 (0)	0/933 (0)	0/43 (0)
TOP3A	7/4168 (0.17)	0/933 (0)	0/43 (0)
USP3	12/4168 (0.29)	12/933 (1.29)	0/43 (0)
USP47	3/4168 (0.07)	1/933 (0.11)	0/43 (0)

*Total number of mutated samples versus total number of samples analyzed in each subtype; Percent of mutated samples is shown in parentheses; Mutations were limited to frameshift insertions/deletions, missense, nonsense and complex mutations types; *SIRT1* is mutated in non-hematological malignancies

Supplemental Table S7. List of primers used for quantitative PCR.

Gene	Primer
Cdkn1a (p21)-F	TTGTCGCTGTCTTGCACTCTGGT
Cdkn1a (p21)-R	AGACCAATCTGCGCTTGGAGTGAT
Cdkn2a (Ink4a)-F	AACTCTTTCGGTCGTACCCC
Cdkn2a (Ink4a)-R	GCGTGCTTGAGCTGAAGCTA
Trp53-F	AAAGGATGCCCATGCTACAGAGGA
Trp53-R	ATGGGAGCTAGCAGTTTGGGCTTT
18S-F	CGCCGCTAGAGGTGAAATTCT
18S-R	CGAACCTCCGACTTTCGTTCT