Supplementary Table 1. Assessment of Baseline Characteristics in Patients of European Ancestry (Discovery and Replication Patient Populations)

Patient Characteristics[a]	Stage 1– Discovery Canadian Patient Population (n = 280 patients)			Stage 2 – Replication Dutch Patient Population (n = 96 patients)			Combined European Patient Population (n = 376 patients)		
	Cases (n = 32)	Controls (n = 248)	*P*	Cases (n = 22)	Controls (n = 74)	*P*	Cases (n = 54)	Controls (n = 322)	*P*
Age at the Start of Treatment Age in yrs, median (IQ range)	9.0 (2.5 – 14)	4 (2 – 7.5)	**0.004**[e]	7.5 (5 – 12)	11 (6 – 14)	0.14	8.5 (4 – 14)	5 (2 – 10)	**0.007**
Gender, female/male (% female)	17/15 (53.1)	112/136 (45.2)	0.45	10/12 (45.5)	36/38 (48.6)	0.81	27/27 (50)	148/174 (46)	0.66
Cumulative Anthracycline Exposure Dose[b] in mg/m^2, median (Interquartile range)	260 (177.5 – 365)	175 (140 – 295)	**0.011**	407.5 (270 – 480)	277.5 (180 – 364)	**0.010**	281.5 (200 – 450)	200 (150 – 300)	**< 0.0001**
Chemotherapy (Anthracycline type[c]), no. (%)									
Doxorubicin	25 (78.1)	178 (71.8)	0.53	13 (59.1)	40 (54.1)	0.81	38 (70.4)	218 (67.7)	0.75
Daunorubicin	2 (6.3)	26 (10.5)	0.75	1 (4.5)	7 (9.5)	0.68	3 (5.6)	33 (10.2)	0.45
Doxorubicin plus daunorubicin	2 (6.3)	37 (14.9)	0.28	0 (0)	4 (5.4)	0.57	2 (3.7)	41 (12.7)	0.063
Doxorubicin plus other	0 (0)	1 (0.4)	1.0	2 (9.1)	7 (9.5)	1.0	2 (3.7)	8 (2.5)	0.64
Daunorubicin plus other	3 (9.4)	6 (2.4)	0.071	0 (0)	0 (0)	0.57	3 (5.6)	6 (1.9)	0.13
Epirubicin	0 (0)	0 (0)	1.0	5 (22.7)	13 (17.6)	0.55	5 (9.3)	13 (4)	0.16
Epirubicin plus other	0 (0)	0 (0)	1.0	1 (4.5)	2 (2.7)	0.55	1 (1.9)	2 (0.6)	0.37
Other[c]	0 (0)	0 (0)	1.0	0 (0)	1 (1.4)	1.0	0 (0)	1 (0.3)	1.0
Primary Diagnosis (Tumor type), no. (%)									
Acute Lymphoblastic Leukemia	5 (15.6)	105 (42.3)	**0.0035**	5 (22.7)	13 (17.6)	0.55	10 (18.5)	118 (36.6)	**0.0085**
Acute Myelogenous Leukemia	3 (9.4)	8 (3.2)	0.12	0 (0)	7 (9.5)	0.35	3 (5.6)	15 (4.7)	0.73
Other Leukemia	0 (0)	4 (1.6)	1.0	0 (0)	1 (1.4)	1.0	0 (0)	5 (1.6)	1.0
Hodgkin's Lymphoma	4 (12.5)	19 (7.7)	0.31	1 (4.5)	8 (10.8)	0.68	5 (9.3)	27 (8.4)	0.79
Non-Hodgkin's Lymphoma	3 (9.4)	23 (9.3)	1.0	6 (27.3)	16 (21.6)	0.57	9 (16.7)	39 (12.1)	0.38
Osteosarcoma	0 (0)	11 (4.4)	0.62	0 (0)	9 (12.2)	0.11	0 (0)	20 (6.2)	0.093
Rhabdomyosarcoma	2 (6.3)	2 (0.8)	**0.066**	3 (13.6)	3 (4.1)	0.13	5 (9.3)	5 (1.6)	**0.0073**
Ewing's sarcoma	5 (15.6)	8 (3.2)	**0.0095**	4 (18.2)	5 (6.8)	0.20	9 (16.7)	13 (4)	**0.0015**
Other sarcoma	1 (3.1)	3 (1.2)	0.39	0 (0)	1 (1.4)	1.0	1 (1.9)	4 (1.2)	0.54
Hepatoblastoma	2 (6.3)	11 (4.4)	0.65	0 (0)	0 (0)	1.0	2 (3.7)	11 (3.4)	1.0
Neuroblastoma	1 (3.1)	28 (11.3)	0.22	0 (0)	0 (0)	1.0	1 (1.9)	28 (8.7)	0.099
Wilms Tumor	6 (18.8)	26 (10.5)	0.23	3 (13.6)	11 (14.9)	1.0	9 (16.7)	37 (11.5)	0.27
Radiotherapy involving the heart[d], no. (%)	12 (37.5)	40 (16.1)	**0.0068**	6 (27.3)	18 (24.3)	0.78	18 (33.3)	58 (18.0)	**0.016**
Use of cardioprotectants, no. (%)	2 (6.3)	7 (2.8)	0.27	0 (0.0)	2 (2.7)	1.0	2 (3.7)	9 (2.8)	0.66
Duration of Follow-up in years, median (range)	7.5 (2.5 – 15.5)	9 (7 – 12)	0.33	22 (19 – 25)	17 (14 – 22)	0.012	15.5 (7 – 22)	10 (7 – 15)	0.021

[a] Age, dose and duration of follow-up were analyzed by Wilcoxon-Mann-Whitney U test. Gender, anthracycline type, tumor type, radiotherapy involving the heart and use of cardioprotectant were analyzed by Fisher exact test. [b] Cumulative anthracycline dose in doxorubicin isotoxic equivalent doses. [c] Other anthracycline type included idarubicin, epirubicin or mitoxantrone.
[d] Includes mantle and mediastinal radiation, whole lung radiation, whole or upper abdominal radiation, left sided flank radiation and total body irradiation. [e] Bold font indicates statistically significant *P* value ($P < 0.05$) and covariates for logistic regression.

Supplementary Table 2. Genome-Wide Association Study of ACT in Patients of European Ancestry: Pharmacogenomic Discovery and Replication Analyses

Pharmacogenomic Associations of Anthracycline Cardiotoxicity						Stage 1 – Discovery Canadian Patient Population n = 280 (32 cases; 248 controls)[a]				Stage 2 – Replication Dutch Patient Population n = 96 (22 cases; 74 controls)[b]			
Variant[c]	Chr[d]	Position[e]	Genomic Region	Function	Minor Allele	*P*	Odds Ratio (95%CI)	MAF (Cases)	MAF (Controls)	*P*	Odds Ratio (95%CI)	MAF (Cases)	MAF (Controls)
rs6895189	5	13430225	*CTNND2* | *DNAH5*	INTERGENIC	C	2.4×10^{-6}	6.1 (2.8 – 13.3)	0.359	0.105	N/A[f]	N/A	N/A	N/A
rs7731918	5	13397992	*CTNND2* | *DNAH5*	INTERGENIC	A	4.0×10^{-6}	5.9 (2.7 – 12.9)	0.355	0.105	0.98	1.0 (0.34 – 3.0)	0.114	0.115
rs2081944	5	13405946	*CTNND2* | *DNAH5*	INTERGENIC	A	4.8×10^{-6}	5.8 (2.6 – 12.7)	0.355	0.105	LD[g]	LD	LD	LD
rs10085086	5	13424707	*CTNND2* | *DNAH5*	INTERGENIC	C	3.6×10^{-6}	5.9 (2.7 – 13.0)	0.355	0.103	LD	LD	LD	LD
rs15736	21	44273858	*WDR4*	NONSYN-CODING	A	2.6×10^{-6}	4.4 (2.2 – 8.7)	0.703	0.366	0.44	0.76 (0.38 – 1.5)	0.386	0.431
rs6586252	21	44276387	*WDR4*	INTRON	A	2.6×10^{-6}	4.4 (2.2 – 8.8)	0.703	0.367	LD	LD	LD	LD
rs8133752	21	44271989	*WDR4*	INTRON	A	3.3×10^{-6}	4.4 (2.2 – 8.6)	0.703	0.370	LD	LD	LD	LD
rs4381672	18	22712791	*ZNF521*	INTRON	A	2.9×10^{-6}	4.3 (2.2 – 8.3)	0.597	0.342	0.78	0.89 (0.40 – 2.0)	0.341	0.372
rs4275929	18	22706688	*ZNF521*	INTRON	C	2.8×10^{-6}	4.3 (2.2 – 8.5)	0.594	0.343	LD	LD	LD	LD
rs4519409	18	22722077	*ZNF521*	INTRON	A	5.6×10^{-6}	4.8 (2.3 – 10.0)	0.516	0.313	LD	LD	LD	LD
rs358224[h]	4	22860785	*GBA3* | *PPARGC1A*	INTERGENIC	A	3.3×10^{-6}	4.2 (2.2 – 8.1)	0.500	0.249	0.47	1.4 (0.56 – 3.5)	0.289	0.217
rs412218	4	22843458	*GBA3* | *PPARGC1A*	INTERGENIC	C	5.7×10^{-6}	4 (2.1 – 7.5)	0.531	0.270	LD	LD	LD	LD
rs11946006	4	22850202	*GBA3* | *PPARGC1A*	INTERGENIC	G	9.1×10^{-6}	3.9 (2.1 – 7.4)	0.531	0.282	LD	LD	LD	LD
rs7676830[i]	4	23169854	*GBA3* | *PPARGC1A*	INTERGENIC	G	5.5×10^{-6}	4.8 (2.3 – 9.8)	0.500	0.262	0.057	2.3 (0.96 – 5.4)	0.364	0.243
rs2282889	7	21476188	*SP4*	INTRON	A	4.4×10^{-6}	0.2 (0.088 – 0.44)	0.234	0.446	0.75	0.9 (0.44 – 1.8)	0.364	0.401
rs2229774[j]	**12**	**53605545**	***RARG***	**NONSYN-CODING**	**A**	**5.0×10^{-6}**	**7 (2.9 – 17)**	**0.297**	**0.081**	**0.0043**	**4.1 (1.5 – 11.5)**	**0.250**	**0.061**
rs9323880	14	93129810	*RIN3*	INTRON	A	6.8×10^{-6}	4.2 (2.1 – 8.2)	0.594	0.348	0.17	1.6 (0.82 – 3.1)	0.50	0.372
rs7042745	9	27248177	*NCRNA00032*	INTRON	A	7.5×10^{-6}	4.5 (2.2 – 8.9)	0.484	0.222	0.65	0.85 (0.41 – 1.8)	0.295	0.319

[a] Covariates for the Logistic regression were age at treatment, cumulative anthracycline exposure, radiotherapy involving the heart and tumour type (acute lymphoblastic leukemia, rhabdomyosarcoma and Ewing's sarcoma).

[b] Covariate for the Logistic regression was cumulative anthracycline exposure.

[c] Variants with $P < 1.0 \times 10^{-5}$ in the discovery GWAS analysis[47].

[d] Chr, chromosome.

[e] Chromosomal positions in the GRCH37.p13.

[f] Not Applicable; call rates for this SNP were < 90% in the Stage 2 cohort.

[g] LD ($r^2 > 0.9$ and D' > 0.9 in the CEU component of HapMap), therefore only 9 of 18 variants were genotyped in the Stage 2 – Replication Dutch patient population.

[h] The call rate for this SNP was 92% in the replication cohort.

[i] Tags a distinct LD block in this genomic region.

[j] Bold font indicates statistically significant SNP after multiple testing correction (discovery $P < 1.0 \times 10^{-5}$ and replication $P < 0.05/9$ LD blocks = 0.006).

Supplementary Table 3. Top GWAS Associations by Cumulative Anthracycline Exposure

Pharmacogenomic Associations of Anthracycline Cardiotoxicity			Low-to-moderate Anthracycline Exposure (≤ 250 mg/m^2)[a]		High Anthracycline Exposure (> 250 mg/m^2)[a]	
Variant[b]	Genomic Regions	Function	**Stage 1: Discovery**[c,d] n = 184 patients (16 cases; 168 controls)	**Stage 2: Replication**[c,e] n = 38 patients (5 cases; 33 controls)	**Stage 1: Discovery**[c,f] n = 96 patients (16 cases; 80 controls)	**Stage 2: Replication**[c,e] n = 58 patients (17 cases; 41 controls)
rs7731918	*CTNND2* | *DNAH5*	INTERGENIC	0.00016	0.70	0.0010	0.85
rs15736	*WDR4*	NONSYN-CODING	0.0011	0.62	0.00029	0.59
rs4381672	*ZNF521*	INTRON	6.9×10^{-5}	0.29	0.021	0.56
rs358224	*GBA3* | *PPARGC1A*	INTERGENIC	0.00020	0.37	0.0065	0.69
rs7676830[g]	*GBA3* | *PPARGC1A*	INTERGENIC	9.1×10^{-5}	0.0240	0.0076	0.30
rs2282889	*SP4*	INTRON	0.0037	0.84	0.00041	(0.05)[h]
rs2229774	*RARG*	NONSYN-CODING	0.00041	0.0036	0.0021	0.084
rs9323880	*RIN3*	INTRON	5.8×10^{-7}	0.76	0.31	0.15
rs7042745	*NCRNA00032*	INTRON	0.0011	0.84	0.0011	0.67

[a] Stratification by cumulative anthracycline exposure as previously performed[6,14,53].
[b] Variants with $P < 1.0 \times 10^{-5}$ in the discovery GWAS analysis[47].
[c] *P*-values are for logistic regression (additive model) with adjustment for covariates.
[d] Covariates for the Logistic regression were age at treatment, cumulative anthracycline exposure, radiotherapy involving the heart and acute lymphoblastic leukemia tumor type.
[e] Covariate for the Logistic regression was cumulative anthracycline exposure.
[f] Covariates for the Logistic regression were age at treatment, cumulative anthracycline exposure, radiotherapy involving the heart and tumor type (acute lymphoblastic leukemia, rhabdomyosarcoma and Ewing's sarcoma).
[g] Tags a distinct LD block in this genomic region.
[h] Regression failed due to absence of variant in cases in this stratified dose group, genotypic testing *P*-value shown.

Supplementary Table 4. Assessment of Baseline Characteristics in Non-European Patient Populations

Patient Characteristics[a]	Hispanic USA – Stanford (n = 23 patients)			African – CPNDS (n = 11 patients)			East Asian – CPNDS (n = 31 patients)			Aboriginal Canadians – CPNDS (n = 15 patients)		
	Cases (n= 5)	Controls (n = 18)	*P*	Cases (n = 2)	Controls (n = 9)	*P*	Cases (n = 8)	Controls (n = 23)	*P*	Cases (n = 4)	Controls (n = 11)	*P*
Age at the Start of Treatment Age in yrs, median (Interquartile range)	14.0 (12.5–17.5)	5.5 (3 – 12)	**0.019**[e]	4.5 (4 – 5)	4.0 (1.5 – 7.0)	0.73	3.5 (0.5 – 8)	6.0 (2.5 – 9.5)	0.32	3.5 (1.5 – 5.5)	4 (2.5 – 7)	0.49
Gender, female/male (% female)	1/4 (20.0)	7/11 (38.9)	0.62	0/2 (0)	6/3 (66.7)	1.0	5/3 (62.5)	11/12 (47.8)	0.69	4/0 (100.0)	6/5 (54.5)	0.23
Cumulative Anthracycline Exposure Dose[b] in mg/m^2, median (Interquartile range)	200 (141–245)	162.5 (150 – 300)	0.80	319.5 (240 – 399)	240 (114 – 382.5)	0.58	300.5 (270.0 – 362.5)	290 (162.5 – 360)	0.46	250 (137.5 – 330)	150 (135 – 245)	0.66
Anthracycline type[c], no. (%)												
Doxorubicin	2 (40)	13 (72.2)	0.30	2 (100)	6 (66.7)	1.0	5 (62.5)	14 (60.9)	1.0	2 (50)	9 (81.8)	0.52
Daunorubicin	1 (20)	2 (11.1)	0.54	0 (0)	2 (22.2)	1.0	1 (12.5)	1 (4.3)	0.46	2 (50)	1 (9.1)	0.15
Doxorubicin plus daunorubicin	2 (40)	3 (16.7)	0.29	0 (0)	1 (11.1)	1.0	0 (0)	5 (21.7)	0.29	0 (0)	1 (9.1)	1.0
Daunorubicin plus other	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.0	2 (25)	2 (8.7)	0.27	0 (0)	0 (0)	1.0
Doxorubicin plus daunorubicin plus others	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.0	0 (0)	1 (4.3)	1.0	0 (0)	0 (0)	1.0
Primary Diagnosis, no. (%)												
Acute Lymphoblastic Leukemia	2 (40)	13 (72.2)	0.30	1 (50)	3 (33.3)	1.0	0 (0)	8 (34.8)	0.076	2 (50)	5 (45.5)	1.0
Acute Myelogenous Leukemia	1 (20)	2 (11.1)	0.54	0 (0)	0 (0)	1.0	2 (25)	2 (8.7)	0.27	1 (25)	0 (0)	0.27
Other Leukemia	2 (40)	3 (16.7)	0.29	0 (0)	0 (0)	1.0	1 (12.5)	0 (0)	0.26	0 (0)	0 (0)	1.0
Hodgkin's Lymphoma	0 (0)	0 (0)	1.0	0 (0)	1 (11.1)	1.0	0 (0)	0 (0)	1.0	0 (0)	1 (9.1)	1.0
Non-Hodgkin's Lymphoma	0 (0)	0 (0)	1.0	0 (0)	1 (11.1)	1.0	2 (25)	3 (13)	0.58	0 (0)	1 (9.1)	1.0
Osteosarcoma	0 (0)	0 (0)	1.0	0 (0)	1 (11.1)	1.0	0 (0)	3 (13)	0.55	0 (0)	1 (9.1)	1.0
Rhabdomyosarcoma	0 (0)	0 (0)	1.0	1 (50)	0 (0)	0.18	0 (0)	1 (4.3)	1.0	0 (0)	0 (0)	1.0
Ewing's sarcoma	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.0	0 (0)	1 (9.1)	1.0
Hepatoblastoma	0 (0)	0 (0)	1.0	0 (0)	0 (0)	1.0	2 (25)	2 (8.7)	0.27	0 (0)	1 (9.1)	1.0
Neuroblastoma	0(0)	0 (0)	1.0	0 (0)	0 (0)	1.0	1 (12.5)	3 (13)	1.0	0 (0)	1 (9.1)	1.0
Wilms Tumor	0 (0)	0 (0)	1.0	0 (0)	3 (33.3)	1.0	0 (0)	1 (4.3)	1.0	1 (25)	0 (0)	0.27
Radiotherapy involving heart[d], no. (%)	Data not available for all patients			0 (0)	2 (22.2)	1.0	0 (0)	0 (0)	1.0	1 (25.0)	0 (0)	0.27
Use of cardioprotectants, no. (%)	Data not available for all patients			0 (0)	0 (0)	1.0	0 (0)	2 (8.7)	1.0	0 (0)	0 (0)	1.0
Duration of Follow-up in years median (range)	4 (3 – 4)	6 (5 – 7)		10.5 (9 – 12)	8 (6.5 – 10.5)	0.33	8.5 (4 – 14)	7 (6.5 – 8)	0.84	7 (2 – 19)	7 (6.5 – 10)	0.85

[a] Age, dose and follow-up were analyzed by Wilcoxon-Mann-Whitney U test. Gender, anthracycline type, tumor type, radiotherapy involving the heart, and use of cardioprotectant were analyzed by Fisher exact test. [b] Cumulative anthracycline dose in doxorubicin isotoxic equivalent doses. [c] Other anthracycline type included idarubicin, epirubicin or mitoxantrone.
[d] Radiotherapy involving the heart include: mantle and mediastinal radiation, whole lung radiation, whole or upper abdominal radiation, left sided flank radiation and total body irradiation
[e] Bold indicates statistically significant *P*-value ($P < 0.05$).

Supplementary Table 5. Association of *RARG* rs2229774 with ACT in Non-European Populations

	Africans n = 11 patients (2 cases; 9 controls)	**Hispanics** n = 23 patients (5 cases;18 controls)	**East Asians** n = 31 patients (8 cases; 23 controls)	**Aboriginal Canadians** n = 15 patients (4 cases; 11 controls)	**Combined** n = 80 patients (19 cases; 61 controls)
MAF[a,b]					
Expected	11.0%	5.0%	0%	Unreported	N/A
Range	6.0% – 16.0%	3.0% – 8.0%	0%	Unreported	N/A
Genetic Association					
Observed MAF (Cases vs. Controls)	25.0% vs. 0%	20.0% vs. 0%	6.3% vs. 0%	25.0% vs. 0%	15.8% vs. 0%
P[c]	0.026	0.052	0.085	0.012	1.2×10^{-4}

[a] MAF are from http://www.1000genomes.org.

[b] Abbreviations: MAF, minor allele frequency; N/A, not applicable.

[c] *P*-values are for genotypic association tests.

Supplementary Table 6: Stage 1 Discovery Analysis – Results for Previous ACT-associated Regions

Marker	Chr[a]	Position[b]	Gene	Function	*P*-value[c]	Odds Ratio (95%CI)	Minor Allele	MAF (32 Cases)	MAF (248 Controls)	Reference
rs17583889	2	138746039	*HNMT*	INTRON	**0.008**	2.4 (1.3 – 4.5)	A	0.344	0.175	12,22
rs8187710	10	101611294	*ABCC2/MRP2*	NONSYN-CODING	**0.021**	4.3 (1.4 – 13.8)	A	0.078	0.046	4,16
rs2868177	7	75589903	*POR*	INTRON	**0.016**	2.1 (1.1 – 4.0)	G	0.438	0.312	8
rs13240755	7	75606109	*POR*	INTRON	**0.033**	2.0 (1.0 – 3.7)	G	0.453	0.349	8
rs4732513	7	75607608	*POR*	INTRON	**0.041**	1.9 (1.0 – 3.6)	G	0.466	0.348	8
rs2232228	16	69143577	*HAS3*	NONSYN-CODING	0.18	0.67 (0.36 – 1.2)	G	0.375	0.427	14
rs3743527	16	16235681	*ABCC1/MRP1*	UTR	0.24	0.65 (0.30 – 1.4)	A	0.172	0.204	11
rs13058338	22	37632770	*RAC2*	INTRON	0.28	0.68 (0.34 – 1.4)	T	0.188	0.245	4,16
rs10836235	11	34460704	*CAT*	INTRON	0.46	0.70 (0.26 – 1.9)	A	0.109	0.118	9
rs1695	11	67352689	*GSTP1*	SYN-CODING	0.46	1.3 (0.68 – 2.4)	G	0.344	0.349	15,17,21
rs1056892	21	37518706	*CBR3*	SYN-CODING	0.64	0.85 (0.42 – 1.7)	A	0.344	0.351	5,6,17,18
rs246221	16	16138322	*ABCC1/MRP1*	NONSYN-CODING	0.68	1.1 (0.60 – 2.2)	G	0.281	0.274	11
rs1799945	6	26091179	*HFE*	NONSYN-CODING	0.68	0.84 (0.37 – 1.9)	G	0.125	0.151	4,20
rs4673	16	88713236	*CYBA*	SYN-CODING	0.81	1.1 (0.59 – 2.0)	A	0.371	0.356	16,19

[a] Abbreviations: Chr, chromosome; MAF, minor allele frequency.
[b] Chromosomal positions in the GRCH37.p13.
[c] *P*-values and odds ratios (95%CI) are for logistic regression analysis (additive model) with adjustment for age at treatment, cumulative anthracycline exposure, radiotherapy involving the heart and incidence of acute lymphoblastic leukemia, rhabdomyosarcoma and Ewing's sarcoma.

Supplementary Table 7. Primers used in this study

Primer Name	Sequence (5' to 3')
*RARG*S427Lfor	ttgaggatgactccttgcagcctggtccc
*RARG*S427Lrev	gggaccaggctgcaaggagtcatcctcaa