No Evidence That G6PD Deficiency Affects the Efficacy or Hematologic Safety of Daunorubicin in Acute Lymphoblastic Leukemia Induction Therapy

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Supporting Information

Supporting Information Table S1 Prognostic Factors at Diagnosis for St. Jude Cohorts

		G6PD Normal	(%)	G6PD Deficient	(%)	*P*-value
Race	Black	115	16.34%	13	59.1%	
	Hispanic	78	11.08%	0	0.0%	
	Other	57	8.10%	4	18.2%	
	White	454	64.49%	5	22.7%	2.6×10^{-6}
Age (years)	≥10	202	28.69%	7	31.8%	
	<10	502	71.31%	15	68.2%	0.81
WBC (cells/ml)	$\geq 50 \times 10^9$	152	21.59%	3	13.6%	
	$<50 \times 10^9$	552	78.41%	19	86.4%	0.60
DNA Index	≥1.16	172	24.43%	16	72.7%	
	<1.16	532	75.57%	6	27.3%	0.80
Lineage	B	580	82.39%	21	95.5%	
	T	124	17.61%	1	4.5%	0.151

Supporting Information Table S2 G6PD Status and Day 15/19 MRD at 2 Different MRD Thresholds in St Jude Cohorts.

Protocol	G6PD Status	MRD ≥ 1% (n (%))	MRD < 1% (n (%))	Total number of patients	*P*-value (Fisher's Exact)
All patients	Deficient	6 (30.0%)	14 (70.0%)	20	
	Normal	201 (28.7%)	499 (71.3%)	700	1
Total XV	Deficient	1 (16.7%)	5 (83.3%)	6	
	Normal	38 (22.6%)	130 (77.4%)	168	1
Total XVI	Deficient	5 (35.7%)	9 (64.3%)	14	
	Normal	163 (30.6%)	369 (69.4%)	532	0.77
Std/High Risk	Deficient	4 (50.0%)	4 (50.0%)	8	
	Normal	137(42.8%)	183 (57.2%)	320	0.73
Low Risk	Deficient	2 (16.7%)	10 (83.3%)	12	
	Normal	64 (16.8%)	316 (83.2%)	380	1
Blacks Only	Deficient	4 (33.3%)	8 (66.7%)	12	
	Normal	39 (32.2%)	82 (67.8%)	121	1
Males Only	Deficient	4 (33.3%)	8 (66.7%)	12	
	Normal	121 (30.2%)	279 (69.8%)	400	0.76
Females Only	Deficient	2 (25.0%)	6 (75.0%)	8	
	Normal	80 (26.7%)	220 (73.3%)	300	1

Protocol	G6PD Status	MRD ≥ 0.1% (n (%))	MRD < 0.1% (n (%))	Total number of patients	*P*-value (Fisher's Exact)
All patients	Deficient	16 (80.0)	4 (20.0%)	20	
	Normal	469 (67.0%)	231 (33.0%)	700	0.33
Total XV	Deficient	4 (66.7%)	2 (33.3%)	6	
	Normal	105 (62.5%)	63 (37.5%)	168	1
Total XVI	Deficient	12 (85.7%)	2 (14.3%)	14	
	Normal	364 (68.4%)	168 (31.6%)	532	0.24
Std/High Risk	Deficient	8 (100%)	0	8	
	Normal	247 (77.2%)	73 (22.8%)	320	0.21
Low Risk	Deficient	8 (66.7%)	4 (33.3%)	12	
	Normal	222 (58.5%)	158 (41.5%)	380	0.77
Blacks	Deficient	10 (83.3%)	2 (16.7%)	12	
	Normal	78 (64.5%)	43 (35.5%)	121	0.34
Males	Deficient	10 (83.3)	2 (16.7%)	12	
	Normal	274 (68.5%)	126 (31.5%)	400	0.36
Females	Deficient	6 (75.0)	2 (25.0%)	8	
	Normal	195 (65.0%)	105 (35.0%)	300	0.72

Supporting Information Table S3 G6PD Status and End of Induction MRD in St Jude Cohorts.

Protocol	G6PD Status	MRD ≥ 0.01% (n (%))	MRD <0.01% (n (%))	Total number of patients	*P*-value (Fisher's Exact)
All patients	Deficient	2 (9.1%)	20 (90.9%)	22	
	Normal	104 (14.9%)	592 (85.1%)	696	0.76
Total XV	Deficient	0 (0%)	6 (100%)	6	
	Normal	35 (21.1%)	131 (78.9%)	166	0.35
Total XVI	Deficient	2 (12.5%)	14 (87.5%)	16	
	Normal	69 (13.0%)	461 (87.0%)	530	1
Std/High Risk	Deficient	1 (11.1%)	8 (88.9%)	9	
	Normal	72 (22.5%)	244 (77.5%)	316	0.69
Low Risk	Deficient	1 (7.7%)	12 (92.3%)	13	
	Normal	32 (8.4%)	348 (91.6%)	380	1
Blacks	Deficient	2 (15.4%)	11 (84.6%)	13	
	Normal	19 (15.8%)	101 (84.2%)	120	1
Males	Deficient	1 (7.1%)	13 (92.9%)	14	
	Normal	61 (15.0%)	340 (85.0%)	401	0.70
Females	Deficient	1 (12.5%)	7 (87.5%)	8	
	Normal	43 (14.6%)	252 (85.4%)	295	1

Supporting Information Table S4 Prognostic Factors at Diagnosis in the COG AALL0232 Cohort

		G6PD Normal	(%)	G6PD Deficient	(%)	P-value
Race	Black	55	4.70%	13	65%	
	Hispanic	307	26.20%	3	15%	
	Other	167	14.30%	4	20%	
	White	643	54.80%	0	0%	$4.3x10^{-15}$
Age (years)	≥10	778	66.40%	14	70%	
	<10	394	33.60%	6	30%	0.82
WBC (cells/ml)	$≥50x10^9$	507	43.20%	8	40%	
	$<50x10^9$	665	56.80%	12	60%	0.82
DNA Index	≥1.16	200	17.10%	4	20%	
	<1.16	969	82.90%	16	80%	0.76

Supporting Information Table S5 Minor Allele Frequency (MAF) of SNPs Observed in the *G6PD* Gene in the COG AALL0232 Protocol (Males and Females, n=2139)

Location (hg19, chrX)[a]	dbSNP[b]	Common Name	Amino Acid Substitution	WHO Classification	MAF (all)	MAF whites	MAF blacks	MAF Hispanics	MAF Other
153760923	rs138746997	NA	His412Gln	Unknown	0.00032	0.00059	0	0	0
153761160	rs34193178	Mira d'Aire	Asp380His	Class IV	0.00097	0	0.013	0	0.0022
153761240	rs76723693	A-,968	Leu353Pro	Class III	0.00097	0	0	0.0025	0.0022
153761261	rs370017540	NA	Gly346Asp	Unknown	0.00032	0.00059	0	0	0
153761337	rs137852327	Viangchan	Val321Met	Class II	0.00032	0	0	0	0.0022
153762269	rs782324339	NA	Asp281Asn	Unknown	0.00032	0	0	0.0013	0
153762317	rs782757170	NA	Leu265Phe	Unknown	0.00032	0	0	0	0.0022
153762340	rs137852328	Mexico City	Arg257Gln	Class III	0.00032	0.00059	0	0	0
153762615	rs145247580	NA	Asp224Glu	Unknown	0.00065	0.0012	0	0	0
153763391	rs370918918	NA	Met189Ile	Unknown	0.00032	0.00059	0	0	0
153763402	rs137852313	Ilesha	Glu186Lys	Class III	0.00065	0	0	0.0025	0
153763405	NA	NA	His185Asp	Unknown	0.00032	0	0	0.0013	0
153763485	rs78365220	NA	Leu158Pro	Unknown	0.00032	0.00059	0	0	0
153763492	rs1050829	A	Asn156Asp	Class IV	0.02950	0.00059	0.34	0.018	0.051
153764199	rs781848254	NA	Arg104Cys	Unknown	0.00032	0	0	0.0013	0
153764217	rs1050828	Asahi	Val98Met	Class III	0.013	0	0.17	0.0038	0.024

[a] GRCh37.p13

[b] National Center for Biotechnology Information dbSNP database.

[c] NP_00393.4

[d] Yoshida A, Beutler E, Motusky AG. Human glucose-6-phosphate-dehydrogenase variants. Bulletin of the World Health Organization. 1971; 45(2): 243-53.

Supporting Information Table S6 Minor Allele Frequency (MAF) of SNPs Observed in the *G6PD* Gene in Male Patients in the COG AALL0232 Protocol (n=1193)

Location (hg19, chrX)[a]	dbSNP[b]	Common Name	Amino Acid Substitution	WHO Classification	MAF (all)	MAF whites	MAF blacks	MAF Hispanics	MAF Other
153761240	rs76723693	A-,968	Leu353Pro	Class III	0.0017	0	0	0.0065	0
153761337	rs137852327	Viangchan	Val321Met	Class II	0.00084	0	0	0	0.0058
153763402	rs137852313	Ilesha	Glu186Lys	Class III	0.00084	0	0	0.0032	0
153763485	rs78365220	NA	Leu158Pro	Unknown	0.00084	0.0016	0	0	0
153763492	rs1050829	A	Asn156Asp	Class IV	0.0335	0.0016	0.35	0.023	0.047
153764217	rs1050828	Asahi	Val98Met	Class III	0.0134	0	0.19	0	0.017

[a] GRCh37.p13

[b] National Center for Biotechnology Information dbSNP database.

[c] NP_00393.4

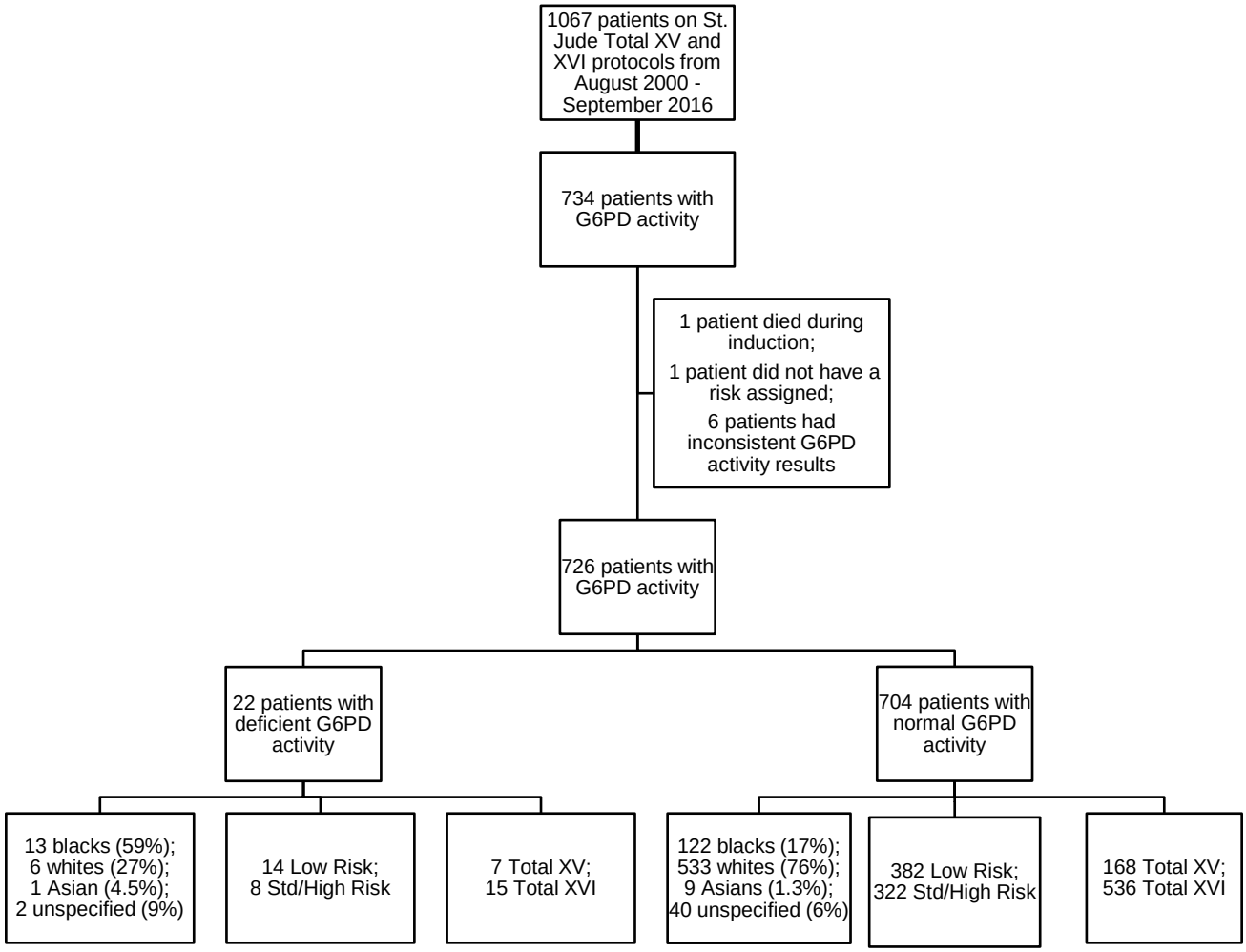
[d] Yoshida A, Beutler E, Motusky AG. Human glucose-6-phosphate-dehydrogenase variants. Bulletin of the World Health Organization. 1971; 45(2): 243-53.

Supporting Information Table S7 *G6PD* genotype and MRD status at Day 29 in COG AALL0232

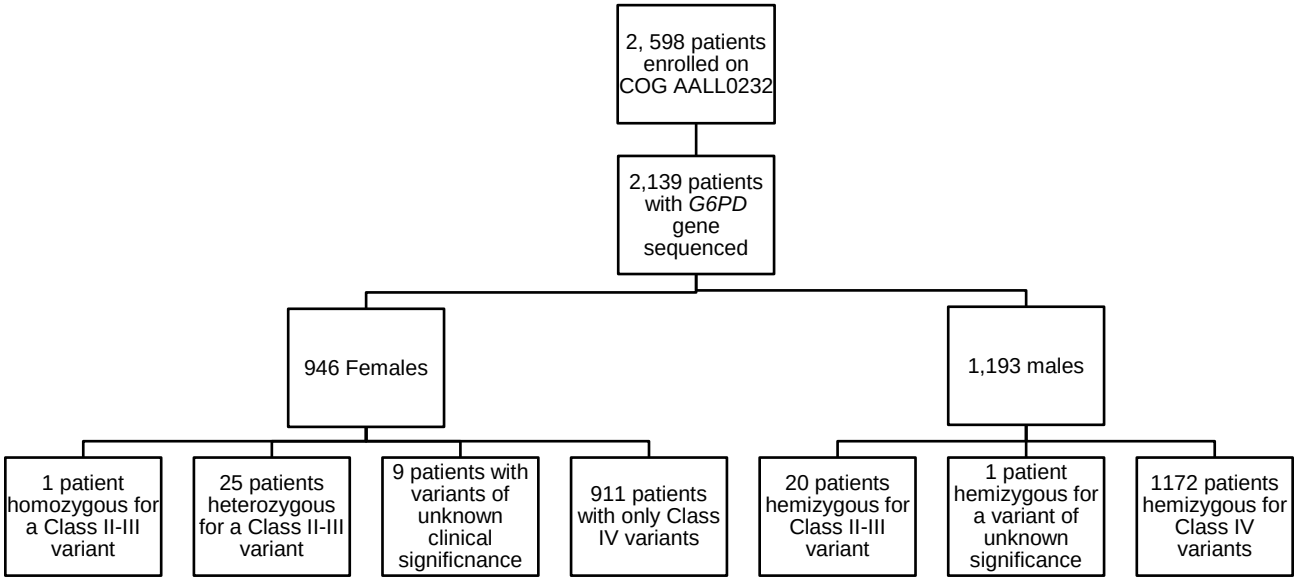
Patients	*G6PD* Genotype Status*	MRD ≥0.1% (n (%))	MRD < 0.1% (n (%))	Total	*P*-value (Fisher's exact)
Males only	Class II-III Allele	3 (15.0%)	17 (85.0%)	20	
	Class IV Allele	242 (20.7%)	930 (79.3%)	1,172	0.78
Non-white males	Class II-III Allele	3 (15.0%)	17 (85.0%)	20	
	Class IV Allele	109 (20.6%)	421 (79.4%)	530	0.78
Females only	Heterozygous for a Class II-III allele	5 (20.0%)	20 (80.0%)	25	
	Homozygous for Class IV Alleles	148 (16.2%)	763 (83.8%)	911	0.58
Non-white females	Heterozygous for a Class II-III Allele	5 (20.8%)	19 (79.2%)	24	
	Homozygous for Class IV Alleles	75 (19.1%)	318 (80.9%)	393	0.79

* Note: no Class I or V alleles were observed

Supporting Information Figure S1. Patient demographics of St. Jude Total XV and Total XVI Cohorts



Supporting Information Figure S2. Patient demographics of COG AALL0232 cohort



Supporting Information Figure S3. *G6PD* genotype does not impact Day 29 MRD in daunorubicin-containing ALL induction therapy in COG AALL0232 protocol. Minimal residual disease (MRD) was assessed by flow cytometry from bone marrow aspirates at day 29, the end of the induction phase, in the COG AALL0232 protocol. There was no difference in MRD ≥ 0.1% vs. <0.1% in patients considered G6PD deficient by genotype compared to patients considered G6PD normal (15% vs. 20.7%, p = 0.78). This held true when the analysis was restricted to non-white patients as well (15% vs. 20.6%, p = 0.78).