

Genomic analysis of venous thrombosis in children with acute lymphoblastic leukemia from diverse ancestries

Yan Zheng,^{1*} Wenjian Yang,^{2*} Jeremie Estepp,^{3,4} Deqing Pei,⁵ Cheng Cheng,⁵ Clifford M. Takemoto,⁴ Hiroto Inaba,⁶ Sima Jeha,^{3,6} Ching-Hon Pui,⁶ Mary V. Relling² and Seth E. Karol⁶

¹Department of Pathology; ²Department of Pharmaceutical Sciences; ³Department of Global Pediatric Medicine; ⁴Department of Hematology; ⁵Department of Biostatistics and ⁶Department of Oncology. St. Jude Children's Research Hospital, Memphis, TN, USA

**YZ and WY contributed equally as first authors.*

Correspondence: S. E. Karol
Seth.Karol@stjude.org

Received: January 22, 2023.

Accepted: June 29, 2023.

Early view: July 6, 2023.

<https://doi.org/10.3324/haematol.2022.281582>

©2024 Ferrata Storti Foundation

Published under a CC BY-NC license



Genomic analysis of venous thrombosis in children with acute lymphoblastic leukemia from diverse ancestries

SUPPLEMENT

Supplemental methods

Total Therapy protocols XV and XVI enrolled patients ages 1-18.99 (Total XV) or birth-18.99 (Total XVI). Therapy included induction therapy with 4 weeks of induction prednisone and 6-9 doses of native L-asparaginase (Total XV) or 1-2 doses of PEGylated L-asparaginase (Total XVI), with additional doses of asparaginase given to patients with high minimal residual disease ($\geq 1\%$ leukemia cells) as assessed by flow cytometry in a bone marrow sample following 2 weeks of remission induction treatment. Post-induction therapy included 2 reinduction phases (with 9 doses of native L-asparaginase in Total XV and 2 doses of PEGylated L-asparaginase in Total XVI during each reinduction) for low-risk patients and 20 (Total XV) or 30 (Total XVI) weeks of continuous asparaginase therapy during early continuation for standard- and high-risk patients.^{1,2}

Patients were genotyped using the Affymetrix GeneChip Human Mapping 500K or SNP6.0 arrays, Illumina HumanExome BeadChip, and whole exome sequencing (WES) using TruSeq Exome Enrichment and Nextera Exome Enrichment kits with paired-end whole-exome sequencing performed using the Illumina HiSeq2500. Additional variants were imputed using Michigan imputation server using phase 1 release v3 of the 1000 Genomes Project as the reference genomes.³ Variant calling for sequencing data utilized the GATK toolkit as previously described.⁴ Single nucleotide polymorphisms (SNPs) with a call rate of $< 90\%$ were excluded. Genetic ancestry was determined as previously described.⁵ Patients with $> 90\%$ European ancestry, $> 60\%$ African ancestry, and more than 10% Hispanic/ Native American ancestry were

categorized into these groups, while patients not meeting any of these criteria were grouped as “other ancestry”.

Supplemental results

Supplemental Table 1: GWAS catalogue SNPs associated with thrombosis

PUBMED ID	MAPPED_GENE	RISK ALLELE	hg19	Meta p-value	Meta OR	95CI lower	95CI upper
31420334	ABO, ABO	rs2519093-T	chr9:136141870-136141870	0.000483	2.07	1.37	3.13
31420334	ADAMTS13, ADAMTS13	rs28446901-?	chr9:136308796-136308796	0.000779	2.07	1.35	3.18
31420334	KNG1, AC068631.1	rs698078-?	chr3:186459227-186459227	0.00229	1.69	1.20	2.38
28203683	LY86	rs3804476-G	chr6:6625704-6625704	0.003839	0.56	0.83	0.37
28011674	B3GAT2 - AL096709.2; B3GAT2	rs2748331-G; rs1304029-A	chr6:71721328-71721328	0.003892	0.52	0.81	0.33
23650146	ABO, ABO	rs687621-G	chr9:136137065-136137065	0.004069	1.72	1.18	2.50
26908601	KNG1, AC068631.1	rs710446-?	chr3:186459927-186459927	0.004173	1.64	1.17	2.31
22672568	ABO - AL772161.2	rs495828-T	chr9:136154867-136154867	0.005755	1.75	1.17	2.60
28203683	LEMD3	rs138916004-G	chr12:65582188-65582188	0.005982	35.3	2.78	448.
21980494	KLKB1 - F11	rs3756008-T	chr4:187185385-187185385	0.008021	1.62	1.13	2.33
31420334	LINC02401, AC084364.4	rs79795993-?	chr12:103961764-103961764	0.008346	0.48	0.83	0.28
33592630	ABO, ABO	rs687289-T	chr9:136137106-136137106	0.010344	1.63	1.12	2.36
23650146	F11	rs4253399-G	chr4:187188094-187188094	0.011375	1.60	1.11	2.32
26908601	FGG - LRAT	rs7654093-T	chr4:155545072-155545072	0.013708	1.63	1.10	2.41
31420334	AC008269.1	rs12473559-?	chr2:207693116-207693116	0.014643	1.78	1.12	2.84
25772935	ABO, ABO	rs529565-C	chr9:136149500-136149500	0.014906	1.58	1.09	2.28
19278955	ABO, ABO	rs505922-C	chr9:136149229-136149229	0.016729	1.56	1.08	2.26
31420334	PEPD	rs4805881-?	chr19:33896432-33896432	0.017622	1.56	1.08	2.26
31420334	AL023495.1	rs191436110-?	chr1:170590770-170590770	0.028319	31.2	1.44	676.
31420334	TC2N, TC2N	rs1884841-A	chr14:92309229-92309229	0.029295	1.47	1.03	2.08
31676865	F11	rs4253417-C	chr4:187199005-187199005	0.030209	1.48	1.03	2.11
28203683	LINC01951 - ARL2BPP6	rs73323772-C	chr5:174680033-174680033	0.030536	0.17	0.84	0.03

21980494	FGA - FGG	rs7659024-A	chr4:155520930-155520930	0.038091	1.51	1.02	2.25
31676865	FGA - FGG	rs2066865-A	chr4:155525276-155525276	0.047358	1.49	1.00	2.21
31420334	FGG	rs2066864-A	chr4:155525695-155525695	0.047358	1.49	1.00	2.21
31420334	F11, F11-AS1	rs2289252-T	chr4:187207381-187207381	0.056655	1.40	0.99	2.00
28203683	ST6GALNAC3	rs61771475-G	chr1:76771276-76771276	0.056932	1.76	0.98	3.18
33592630	KIF26B, KIF26B	rs1756912-A	chr1:245588095-245588095	0.065236	0.43	1.05	0.17
28373160	F11	rs4253416-T	chr4:187197994-187197994	0.065915	0.71	1.02	0.49
31420334	H6PD - SPSB1	rs10746487-?	chr1:9338689-9338689	0.067237	0.64	1.03	0.40
31420334	AL135926.1	rs115063924-?	chr1:168711028-168711028	0.068181	3.80	0.90	16.0
28203683	ZNF71, ZIM2-AS1	rs77926443-T	chr19:57107166-57107166	0.068335	6.62	0.86	50.5
31420334	LINC02476	rs149328960-?	chr7:119252364-119252364	0.068535	1.54	0.96	2.47
32438682	RIC1	rs117233659-?	chr9:5731974-5731974	0.078858	4.49	0.84	24.0
31420334	STX10	rs7508633-G	chr19:13258290-13258290	0.085295	0.72	1.04	0.50
31420334	AL162417.1, GBT1	rs34454320-?	chr9:136032602-136032602	0.086146	0.63	1.06	0.37
31420334	F11	rs2036914-C	chr4:187192481-187192481	0.105696	0.74	1.06	0.51
28203683	RIPK4 - PRDM15	rs111476780-A	chr21:43196052-43196052	0.111381	9.78	0.59	162.
28203683	AL512353.3 - ATP6V1E1P1	rs80091440-A	chr1:43359019-43359019	0.112655	4.00	0.72	22.2
31420334	NAV2	rs150478906-?	chr11:20057391-20057391	0.126698	6.16	0.59	63.5
31420334	PHF21A	rs140876547-?	chr11:45984068-45984068	0.127032	5.90	0.60	57.8
26908601	ICE2P2 - GAPDHP50	rs60942712-T	chr3:89047759-89047759	0.129338	1.56	0.87	2.80
31420334	LINC01681	rs113976843-?	chr1:170223768-170223768	0.13061	2.52	0.75	8.42
31420334	XIRP1 - AC092053.7	rs9880479-?	chr3:39237475-39237475	0.133442	0.61	1.15	0.32
32232851	RUBCNL	rs139968164-?	chr13:46935652-46935652	0.134433	6.30	0.56	70.3
33592630	TSBP1-AS1	rs17202393-A	chr6:32361485-32361485	0.134441	1.44	0.89	2.34
28203683	RPL7P60 - LAMTOR4	rs77686669-C	chr7:99744572-99744572	0.135811	0.70	1.11	0.45
28203683	MAP3K21 - RNU4-77P	rs4492561-G	chr1:233562212-233562212	0.138451	1.30	0.91	1.85
31420334	C4BPA	rs2842700-A	chr1:207282149-207282149	0.147113	1.59	0.84	2.99
28203683	LINC02015	rs74793292-?	chr3:177590409-177590409	0.147857	2.72	0.70	10.5
31420334	IER2	rs55724477-?	chr19:13263055-13263055	0.150714	0.76	1.10	0.53
28011674	B3GAT2	rs1304029-?	chr6:71623253-71623253	0.150957	0.75	1.10	0.51

28203683	JAKMIP2 - SPINK1	rs72835183-A	chr5:147170977-147170977	0.15182	0.48	1.30	0.18
28203683	AC025554.1 - RNU6-224P	rs7696446-G	chr4:132095279-132095279	0.153157	0.75	1.11	0.51
23650146	F5	rs6427196-C	chr1:169481223-169481223	0.158047	1.29	0.90	1.83
31676865	AL118508.1 - AL390037.1	rs6083037-A	chr20:23182559-23182559	0.159839	0.68	1.15	0.41
31420334	F11-AS1, AC018709.1	rs149130695-?	chr4:187385348-187385348	0.165101	1.63	0.81	3.28
32232851	AP003501.1, ROBO4	rs138481093-?	chr11:124756982-124756982	0.166074	3.24	0.61	17.1
31420334	NLRP2	rs1671135-C	chr19:55511873-55511873	0.169308	0.70	1.16	0.42
28203683	MIR4276 - HPGD	rs3846297-T	chr4:175388125-175388125	0.170208	0.61	1.23	0.30
31420334	PLCG2	rs12445050-T	chr16:81870969-81870969	0.172024	1.42	0.85	2.37
32232851	RETREG1	rs78314670-?	chr5:16572153-16572153	0.177305	2.37	0.67	8.38
32232851	MIPEP	rs7327620-?	chr13:24342934-24342934	0.17813	1.84	0.75	4.49
28373160	ABO, ABO	rs8176645-A	chr9:136149098-136149098	0.178442	1.29	0.88	1.89
32232851	H1-2	rs61748580-?	chr6:26056399-26056399	0.201043	2.17	0.66	7.18
31420334	ZFPM2, ZFPM2-AS1	rs4541868-C	chr8:106590705-106590705	0.204206	1.27	0.87	1.84
32232851	Z99572.1 - F5	rs78314670-?	chr1:169477574-169477574	0.205765	1.05	0.97	1.13
28203683	AC005064.1, RELN	rs6956101-G	chr7:103148602-103148602	0.209669	0.72	1.19	0.44
32232851	CCDC93	rs17512204-?	chr2:118732831-118732831	0.212048	1.49	0.79	2.82
31420334	YBX2 - EIF5A	rs12450494-A	chr17:7207887-7207887	0.21342	1.26	0.87	1.82
28203683	CMTM7	rs188198692-C	chr3:32451330-32451330	0.214643	5.91	0.35	97.7
32438682	AL359922.1, MTAP	rs67134687-?	chr9:21845308-21845308	0.214974	0.58	1.36	0.25
28203683	AC132803.1	rs115316316-A	chr5:144493178-144493178	0.226031	6.20	0.32	119.
28203683	OPCML	rs80068859-G	chr11:132494525-132494525	0.227617	4.01	0.41	38.5
28203683	SCD5	rs115533905-T	chr4:83649112-83649112	0.230286	0.59	1.38	0.25
28203683	AP001120.1 - GNAL	rs75695915-A	chr18:11672971-11672971	0.234768	0.57	1.43	0.23
31420334	NUP160 - AC023232.1	rs141237278-?	chr11:47920993-47920993	0.237957	0.34	2.02	0.05
31676865	OSMR-AS1	rs16867574-C	chr5:38708554-38708554	0.23918	0.77	1.18	0.50
31420334	LINC01681 - HAUS4P1	rs12120558-?	chr1:170335828-170335828	0.241151	1.84	0.66	5.10
32232851	AC009132.1 - WDR59	rs16948255-?	chr16:74881820-74881820	0.254842	0.29	2.39	0.03
31420334	HIC1, SMG6	rs1048483-T	chr17:1966457-1966457	0.260555	0.81	1.15	0.57
32438682	CEP41	rs73152871-?	chr7:130043565-130043565	0.260975	1.70	0.67	4.32

28203683	LINC02663 - LINC02670	rs12253502-G	chr10:10022101-10022101	0.263857	3.00	0.43	20.7
28203683	AC100779.1	rs74893887-C	chr18:40704483-40704483	0.265467	2.57	0.48	13.5
31420334	EBF2	rs1021230-?	chr8:25786443-25786443	0.28019	0.78	1.21	0.50
31420334	C1orf112	rs185120584-?	chr1:169659128-169659128	0.281219	1.72	0.64	4.63
31420334	CREB3L1 - DGKZ	rs149903077-?	chr11:46349696-46349696	0.283361	1.81	0.60	5.42
28203683	AC010445.1 - AC010460.3	rs10076419-?	chr5:23223853-23223853	0.287511	1.56	0.68	3.59
32232851	TGM4, TGM4	rs1395388-?	chr3:44948674-44948674	0.289954	0.64	1.44	0.28
28203683	LHPP	rs74160941-T	chr10:126267737-126267737	0.292385	3.99	0.30	52.7
28203683	ICE2P2 - GAPDHP50	rs111293219-T	chr3:89019410-89019410	0.296717	2.44	0.45	13.1
31420334	F2	rs1799963-?	chr11:46761055-46761055	0.308009	1.76	0.59	5.29
31420334	TC2N, TC2N	rs10498632-?	chr14:92290744-92290744	0.310215	1.21	0.83	1.75
31420334	AC128657.1 - TSPAN19	rs35352631-?	chr12:85337112-85337112	0.315327	1.85	0.55	6.16
31676865	ZFPM2, ZFPM2-AS1	rs4734879-A	chr8:106583124-106583124	0.315659	1.18	0.84	1.65
26888256	AP005230.1, AP005262.1	rs28496996-G	chr18:1952127-1952127	0.316503	1.92	0.53	6.97
23650146	SV2C	rs3733860-A	chr5:75622814-75622814	0.321963	0.73	1.35	0.39
32232851	PPARGC1B	rs7732671-?	chr5:149212243-149212243	0.32855	0.62	1.61	0.23
28203683	AC067819.1 - TMX3	rs62097965-T	chr18:66199119-66199119	0.330833	0.61	1.64	0.22
31420334	DCHS2 - AC110753.1	rs4696594-?	chr4:155418647-155418647	0.334062	1.22	0.81	1.82
32438682	SLC24A4 - RIN3	rs140514603-?	chr14:92978298-92978298	0.335742	0.47	2.14	0.10
28203683	ANK3	rs137898089-A	chr10:61790083-61790083	0.33577	1.51	0.65	3.50
31420334	A4GALT	rs5758896-?	chr22:43115576-43115576	0.342447	0.82	1.23	0.55
32438682	AL450992.2	rs4845725-?	chr1:151973800-151973800	0.345357	0.57	1.82	0.18
31420334	OSMR-AS1	rs4869589-T	chr5:38707871-38707871	0.348278	0.81	1.24	0.53
32232851	DDX20	rs41310098-?	chr1:112308722-112308722	0.348628	4.06	0.21	76.3
26888256	AC073115.2	rs73692310-T	chr7:46006655-46006655	0.349918	2.57	0.35	18.6
31420334	ATP1B1	rs145163454-?	chr1:169090748-169090748	0.354868	1.40	0.68	2.87
31420334	STXBP5	rs620715-?	chr6:147570239-147570239	0.35808	1.17	0.83	1.66
28203683	GYPB, AC107223.1	rs9308174-?	chr4:144938730-144938730	0.359104	0.56	1.90	0.17
31420334	NME7	rs1209731-?	chr1:169324793-169324793	0.359889	1.09	0.90	1.33
31420334	AMBRA1	rs147283716-?	chr11:46555222-46555222	0.362344	1.38	0.68	2.80

28203683	AC091074.2	rs1484194-?	chr15:46666190-46666190	0.363784	0.82	1.25	0.54
31420334	AL118508.1	rs117390891-?	chr20:23168526-23168526	0.371022	0.78	1.33	0.46
28203683	GET1-SH3BGR, LCA5L, GET1	rs116694748-G	chr21:40789684-40789684	0.379739	1.85	0.46	7.33
32438682	OVCH2	rs142811167-?	chr11:7719585-7719585	0.385701	1.76	0.48	6.36
31420334	F10	rs3211752-?	chr13:113787459-113787459	0.386312	1.16	0.82	1.64
31420334	GRK5	rs10886430-G	chr10:121010256-121010256	0.388698	1.22	0.77	1.92
31420334	SIGLEC30P - METTL11B	rs12136148-?	chr1:170092671-170092671	0.389122	0.67	1.64	0.27
31420334	PTPRJ	rs117784795-?	chr11:48052066-48052066	0.390086	0.44	2.81	0.07
28203683	AC012494.1	rs191269447-A	chr2:78158334-78158334	0.39611	2.01	0.40	10.1
25772935	PROCR	rs6087685-C	chr20:33777612-33777612	0.399027	0.83	1.26	0.55
31420334	LINC02710 - AC116021.1	rs77662718-?	chr11:46242003-46242003	0.401174	0.72	1.52	0.34
31420334	FNBP4	rs150341456-?	chr11:47783614-47783614	0.402976	0.45	2.89	0.07
32438682	ALOX15B	rs1804772-?	chr17:7952005-7952005	0.409706	0.53	2.37	0.11
33592630	F5	rs6025-A	chr1:169519049-169519049	0.417174	1.17	0.79	1.72
32438682	LINC02355 - IQCM	rs72951801-?	chr4:150207076-150207076	0.418175	1.41	0.60	3.30
31420334	TBC1D5, SATB1	rs115865014-?	chr3:18465750-18465750	0.420057	1.92	0.39	9.50
32438682	ANTXR2	rs7682733-?	chr4:80933225-80933225	0.420887	1.13	0.83	1.52
31420334	AC078778.1, COPZ1	rs7297265-?	chr12:54719689-54719689	0.426617	0.83	1.30	0.53
28203683	PTPRT	rs2208049-T	chr20:41666868-41666868	0.429054	1.17	0.78	1.74
31420334	C11orf49	rs149639773-?	chr11:47109498-47109498	0.430039	1.46	0.56	3.81
31420334	AC090589.1 - DDB2	rs182879407-?	chr11:47220778-47220778	0.430039	1.46	0.56	3.81
23650146	OTUD7A	rs7164569-A	chr15:31793930-31793930	0.432943	0.85	1.26	0.58
28203683	AC087516.1 - AC087516.2	rs115290532-C	chr15:36714606-36714606	0.433325	3.13	0.17	54.6
31420334	LRP4	rs191945075-A	chr11:46933311-46933311	0.434137	1.46	0.56	3.78
31676865	PROCR	rs10747514-A	chr20:33775369-33775369	0.436728	0.85	1.27	0.56
31420334	PROCR	rs6060288-?	chr20:33772243-33772243	0.436728	0.85	1.27	0.56
31420334	PSMC3	rs141325867-?	chr11:47443654-47443654	0.437846	0.52	2.67	0.10
31420334	F9	rs6048-?	chrX:138633280-138633280	0.446016	1.13	0.82	1.54
31420334	AC104232.3 - AC087808.1	rs113451833-?	chr8:65882354-65882354	0.44862	1.17	0.77	1.76
31420334	ABO, ABO	rs8176749-T	chr9:136131188-136131188	0.449741	1.24	0.70	2.21

28203683	AC023137.2 - AC023137.1	rs13390371-A	chr2:20675226- 20675226	0.455156	1.19	0.75	1.88
31420334	LINC01231	rs115405361-?	chr9:3193201- 3193201	0.464252	1.97	0.32	12.1
33592630	AC016987.1, AGBL1	rs72755680-C	chr15:87509243- 87509243	0.46428	0.58	2.49	0.13
32438682	RYK	rs4546143-?	chr3:133785177- 133785177	0.485768	0.87	1.26	0.61
28203683	LINC02651 - RPL5P26	rs10998957-C	chr10:71528930- 71528930	0.491601	0.85	1.34	0.53
32438682	CNTN5	rs17134658-?	chr11:99782640- 99782640	0.493616	0.30	9.00	0.01
32232851	ZNF718	rs144152312-?	chr4:155655- 155655	0.494996	0.53	3.19	0.09
31420334	TRPC4AP	rs76223987-?	chr20:33618472- 33618472	0.495504	0.78	1.56	0.39
32438682	AC106041.1 - HSP90AB2P	rs60440889-?	chr4:13140593- 13140593	0.497401	1.05	0.89	1.24
31420334	S1PR5 - ATG4D	rs12981279-?	chr19:10639533- 10639533	0.499025	1.13	0.79	1.61
32438682	NR2F2-AS1	rs61037031-?	chr15:96852799- 96852799	0.509412	0.84	1.39	0.50
31420334	ATXN7L1	rs28562194-?	chr7:105502606- 105502606	0.509983	0.85	1.35	0.54
28203683	TBC1D4	rs74096215-C	chr13:75869162- 75869162	0.520706	0.45	4.99	0.04
31420334	AHCY - AL356299.2	rs819131-?	chr20:32907849- 32907849	0.528625	0.80	1.57	0.41
32232851	MYHAS, MYH8, AC005323.2	rs111567318-?	chr17:10295914- 10295914	0.530192	1.90	0.25	14.1
31420334	PROCR	rs867186-G	chr20:33764554- 33764554	0.536675	0.81	1.55	0.42
32232851	HRCT1	rs141107455-?	chr9:35906504- 35906504	0.542536	0.45	5.68	0.03
28203683	FAM98A	rs3213961-T	chr2:33811936- 33811936	0.547161	0.86	1.39	0.53
31420334	KIFAP3	rs688565-?	chr1:169941408- 169941408	0.548907	0.68	2.36	0.19
31420334	ITCH	rs77385328-?	chr20:33045092- 33045092	0.549123	0.77	1.80	0.32
31420334	NME7	rs2040445-?	chr1:169216412- 169216412	0.554946	0.97	1.06	0.89
31420334	ST3GAL4	rs142029184-?	chr11:126271608- 126271608	0.558498	0.58	3.48	0.09
31420334	LINC00970, AL135926.1	rs78516619-?	chr1:168889373- 168889373	0.56077	1.61	0.31	8.18
33592630	F5	rs1018827-A	chr1:169514006- 169514006	0.561968	0.83	1.53	0.45
28203683	AP005717.2, DSCC1	rs14027-?	chr8:120846589- 120846589	0.5621	0.89	1.29	0.62
28203683	AC116366.3, RAD50	rs2706345-?	chr5:131903928- 131903928	0.564975	1.13	0.73	1.74
28203683	ABCC1, ABCC1	rs215088-A	chr16:16065401- 16065401	0.571363	0.87	1.39	0.54
23650146	SUSD1	rs4979078-C	chr9:114823121- 114823121	0.576518	0.84	1.54	0.45
33592630	NME7	rs16861990-C	chr1:169135127- 169135127	0.582276	1.06	0.85	1.31
33592630	ST8SIA4 - RN7SL802P	rs115887893-A	chr5:100848341- 100848341	0.5826	1.15	0.69	1.92

31420334	AL157944.1	rs144405847-?	chr1:82807876-82807876	0.593464	1.24	0.55	2.77
31420334	C1orf112	rs12122803-?	chr1:169794505-169794505	0.595107	1.13	0.71	1.80
32438682	AC105417.1 - AC082650.1	rs7677291-?	chr4:130161349-130161349	0.595833	0.90	1.30	0.62
28203683	ANKRD49P3 - RNA5SP193	rs78459308-?	chr5:136210932-136210932	0.602458	0.54	5.34	0.05
31420334	C1orf198	rs145470028-G	chr1:230986407-230986407	0.614534	0.64	3.51	0.11
28203683	UBA6-AS1, TMPRSS11D	rs74316172-G	chr4:68746932-68746932	0.625162	2.33	0.07	69.7
31676865	SLC44A2	rs2288904-G	chr19:10742170-10742170	0.627609	1.10	0.72	1.69
31420334	NUGGC	rs12675621-G	chr8:27898452-27898452	0.629867	1.09	0.76	1.56
28203683	DAPK2	rs332288-T	chr15:64309266-64309266	0.638076	0.60	4.91	0.07
23650146	AC090044.1 - AC087430.1	rs6764623-C	chr3:1046038-1046038	0.638832	1.09	0.75	1.59
31420334	SYT6	rs12732487-?	chr1:114662959-114662959	0.642452	0.86	1.58	0.47
28203683	ITPR3	rs2229637-A	chr6:33643558-33643558	0.64915	0.89	1.45	0.54
28203683	AC012494.1	rs75018958-G	chr2:77882020-77882020	0.668768	0.61	5.62	0.06
31420334	ERCC3	rs4150416-?	chr2:128046548-128046548	0.66956	1.08	0.75	1.54
31420334	F8	rs1800291-?	chrX:154158285-154158285	0.671165	0.89	1.48	0.54
26908601	COX7A2L	rs72798544-G	chr2:42599605-42599605	0.674584	1.23	0.46	3.31
33592630	PSG8	rs59559305-A	chr19:43283623-43283623	0.675842	1.08	0.73	1.59
28203683	TMPRSS11F - FTLP10	rs185537126-A	chr4:69016856-69016856	0.676233	1.91	0.09	40.6
31420334	XCL1 - DPT	rs72705895-?	chr1:168572720-168572720	0.679451	1.15	0.58	2.25
32232851	KRT74	rs139723680-?	chr12:52962050-52962050	0.679676	1.22	0.46	3.27
31420334	SBNO1	rs11057270-?	chr12:123808073-123808073	0.68162	1.07	0.74	1.55
32232851	SRRM2	rs117133016-?	chr16:2816627-2816627	0.683887	1.32	0.34	5.12
28203683	WVOX	rs1875939-G	chr16:79011072-79011072	0.686759	1.00	0.98	1.02
31420334	STXBP5	rs9373523-G	chr6:147701133-147701133	0.691807	1.07	0.74	1.56
31420334	F5	rs4524-T	chr1:169511755-169511755	0.691832	0.92	1.37	0.61
28203683	RN7SL807P - HIGD1AP4	rs2056190-C	chr2:224167879-224167879	0.695116	1.06	0.77	1.46
28203683	AC015574.1	rs80255315-A	chr15:96277148-96277148	0.700014	1.35	0.28	6.47
31420334	NCOA6	rs6088618-?	chr20:33409350-33409350	0.705637	0.93	1.33	0.65
31420334	ANK2	rs41496644-?	chr4:113854560-113854560	0.706354	0.86	1.84	0.40
31420334	NCOA6	rs13044899-?	chr20:33287078-33287078	0.716767	0.93	1.33	0.65

32232851	E2F7	rs310831-?	chr12:77419341-77419341	0.717203	1.09	0.66	1.80
28203683	FRMD1	rs9346649-?	chr6:168490232-168490232	0.730507	0.94	1.29	0.69
28203683	CLMN	rs73333233-T	chr14:95660380-95660380	0.730878	1.04	0.83	1.30
32438682	DDX59-AS1 - CAMSAP2	rs115456075-?	chr1:200674225-200674225	0.733889	1.19	0.42	3.37
32438682	NCALD	rs16868899-?	chr8:103042178-103042178	0.754799	0.87	2.06	0.36
31420334	GRK4	rs192519054-?	chr4:2991907-2991907	0.757793	0.66	8.68	0.05
32232851	AC015631.1, PABPC4L	rs6830036-?	chr4:135121183-135121183	0.766862	1.51	0.09	23.6
28203683	BCL7A	rs7957207-T	chr12:122469395-122469395	0.767619	0.92	1.56	0.54
28203683	VLDLR-AS1	rs12686800-A	chr9:2489728-2489728	0.770303	1.05	0.71	1.56
28203683	ZFP64	rs8120062-A	chr20:50741990-50741990	0.773932	1.06	0.69	1.61
32438682	PKHD1	rs115072237-?	chr6:51523739-51523739	0.780518	0.59	22.5	0.01
31420334	MPHOSPH9	rs2851436-T	chr12:123667354-123667354	0.781251	1.05	0.73	1.50
31420334	OR4A46P - OR4A40P	rs189484085-?	chr11:48533489-48533489	0.783469	1.18	0.35	3.98
28203683	PRKCH	rs17098149-C	chr14:61699772-61699772	0.786882	1.03	0.79	1.34
32438682	LINC02208	rs139018151-?	chr5:117765733-117765733	0.792223	1.23	0.26	5.82
31420334	TSPAN4	rs73403190-?	chr11:855724-855724	0.795645	0.82	3.54	0.19
32438682	FTMT - SRFBP1	rs79055704-?	chr5:121263584-121263584	0.796611	0.73	7.65	0.07
31420334	AL139021.3	rs11158204-C	chr14:58844526-58844526	0.805635	1.04	0.73	1.49
33592630	AC010157.2, NRG3	rs1649936-T	chr10:83969121-83969121	0.807569	1.06	0.63	1.79
28203683	AL138694.1	rs114167228-A	chr13:109003514-109003514	0.808555	1.26	0.18	8.51
31420334	MSRA, MSRA	rs10090114-?	chr8:10004954-10004954	0.80994	0.91	1.91	0.43
33592630	MTND1P3 - MYL6P4	rs145241704-G	chr7:141505087-141505087	0.81218	0.84	3.26	0.22
31420334	F2	rs3136516-G	chr11:46760756-46760756	0.816592	1.04	0.70	1.54
31420334	AC024405.1 - OR4C50P	rs148268781-?	chr11:50623119-50623119	0.816952	1.63	0.02	105.
31420334	FOLH1	rs185558485-?	chr11:49224885-49224885	0.816952	1.63	0.02	105.
31420334	AC136759.1	rs191856980-?	chr11:49681184-49681184	0.816952	1.63	0.02	105.
31420334	GTF2IP11 - AC109635.4	rs147455989-?	chr11:50120568-50120568	0.816952	1.63	0.02	105.
31420334	AC109635.1 - AC109635.5	rs181706792-?	chr11:50224700-50224700	0.816952	1.63	0.02	105.
31420334	TSPAN15	rs78707713-T	chr10:71245276-71245276	0.825628	0.91	1.97	0.42
26908601	TSPAN15	rs17490626-G	chr10:71218646-71218646	0.829032	0.91	1.97	0.42

31420334	NDUFS3, KBTBD4	rs144915398-?	chr11:47598481- 47598481	0.834522	0.75	10.7	0.05
31420334	AC090125.1	rs7245232-?	chr18:71659952- 71659952	0.837814	0.95	1.55	0.58
28203683	TOGARAM2	rs116739666-G	chr2:29201262- 29201262	0.840842	1.31	0.09	18.8
32438682	KALRN	rs570684-?	chr3:124122846- 124122846	0.84201	0.89	2.62	0.30
28203683	CLEC19A	rs115068712-A	chr16:19316811- 19316811	0.844454	1.37	0.05	34.1
33592630	NCAM2	rs62207434-T	chr21:22780048- 22780048	0.845196	0.87	3.31	0.23
31676865	CATSPERB, CATSPERB	rs57328376-G	chr14:92235039- 92235039	0.848724	1.03	0.75	1.39
31420334	STXBP5	rs9390460-?	chr6:147694334- 147694334	0.8494	1.03	0.72	1.47
26908601	AL357518.1 - AL357518.2	rs113092656-A	chr6:11615305- 11615305	0.850738	1.10	0.40	2.99
31420334	AC084851.2 - AC118273.1	rs192463896-?	chr11:49115099- 49115099	0.855458	1.37	0.04	41.7
32438682	MIR3976HG	rs56929051-?	chr18:5856604- 5856604	0.859668	1.07	0.48	2.36
31420334	PSMA3-AS1, ARMH4	rs2180871-?	chr14:58739537- 58739537	0.864449	1.02	0.77	1.35
28203683	DPYSL5	rs12612619-T	chr2:27137671- 27137671	0.866173	1.01	0.81	1.27
31420334	ABCB9	rs4148856-?	chr12:123450765- 123450765	0.877007	0.94	1.90	0.47
31420334	PTPRJ - OR4B1	rs182484222-?	chr11:48211757- 48211757	0.879472	1.05	0.51	2.16
28203683	CTNNBIP1	rs191576341-T	chr1:9927808- 9927808	0.880714	0.87	5.28	0.14
31420334	EDEM2 - PROCR	rs6088735-T	chr20:33745676- 33745676	0.884537	1.03	0.66	1.61
31420334	FAM83C - UQCC1	rs2425051-?	chr20:33880363- 33880363	0.885537	1.03	0.67	1.57
32232851	GEMIN5	rs115551140-?	chr5:154278151- 154278151	0.888894	0.85	8.18	0.08
26888256	AL118508.3 - CD93	rs1998081-T	chr20:23057482- 23057482	0.90023	1.03	0.58	1.83
32232851	PDZD9, PDZD9	rs140219446-?	chr16:21995737- 21995737	0.908505	0.82	21.1	0.03
31420334	CCDC102B - AC090337.1	rs8089640-?	chr18:66853351- 66853351	0.915798	0.98	1.30	0.74
31420334	OR4A44P - AC027369.6	rs181813804-?	chr11:48728256- 48728256	0.915898	1.26	0.01	95.0
31420334	VWF	rs1558519-G	chr12:6153738- 6153738	0.924235	1.01	0.78	1.31
28203683	AL157944.1	rs78810706-T	chr1:82744252- 82744252	0.924406	1.03	0.49	2.16
32232851	TSPOAP1	rs9913145-?	chr17:56389732- 56389732	0.928822	0.96	2.33	0.39
31420334	DNM2	rs143928955-?	chr19:10842733- 10842733	0.929651	0.95	2.83	0.31
26908601	SLC44A2	rs9797861-T	chr19:10743126- 10743126	0.930744	1.01	0.72	1.42
31420334	F11	rs4253421-G	chr4:187204937- 187204937	0.93087	1.03	0.51	2.04
31420334	PLEK	rs1867312-C	chr2:68619981- 68619981	0.938295	0.98	1.43	0.67

31420334	BX284613.2	rs10919507-?	chr1:170854609-170854609	0.939799	0.77	668.	0.00
31420334	SLC44A2	rs4548995-C	chr19:10740871-10740871	0.948273	1.01	0.73	1.39
28203683	AKAP8P1 - AL451129.1	rs113048739-A	chr9:11023588-11023588	0.948977	0.93	8.33	0.10
32438682	USP54	rs143580123-?	chr10:75364534-75364534	0.950747	0.93	7.72	0.11
28203683	TRPM3	rs59300564-T	chr9:73186956-73186956	0.954842	0.93	11.1	0.07
33592630	LINC01293 - POLE4	rs74965230-C	chr2:75182831-75182831	0.957496	0.91	28.0	0.02
31420334	LINC00299	rs409169-?	chr2:8556084-8556084	0.968817	0.98	1.72	0.56
28203683	PRKCE	rs72879760-T	chr2:46373443-46373443	0.972469	0.91	110.	0.00
28203683	ATP6V1G1P7 - AL136524.1	rs6491750-C	chr13:104143612-104143612	0.973702	0.97	5.05	0.18
28203683	LEKR1	rs987724-?	chr3:156683136-156683136	0.975035	1.00	0.62	1.62
32438682	AL359987.1 - LINC02531	rs72926690-?	chr6:93349871-93349871	0.977667	0.95	27.0	0.03
26888256	THBD - AL118508.3	rs2144940-C	chr20:23050806-23050806	0.996759	0.98	930.	0.00
31420334	MCF2L2 - LINC00888	rs59994833-?	chr3:183149321-183149321	0.99748	1.01	0.00	936.
23650146	FGG - LRAT	rs6536024-C	chr4:155543369-155543369	0.998487	1.03	0.00	2560

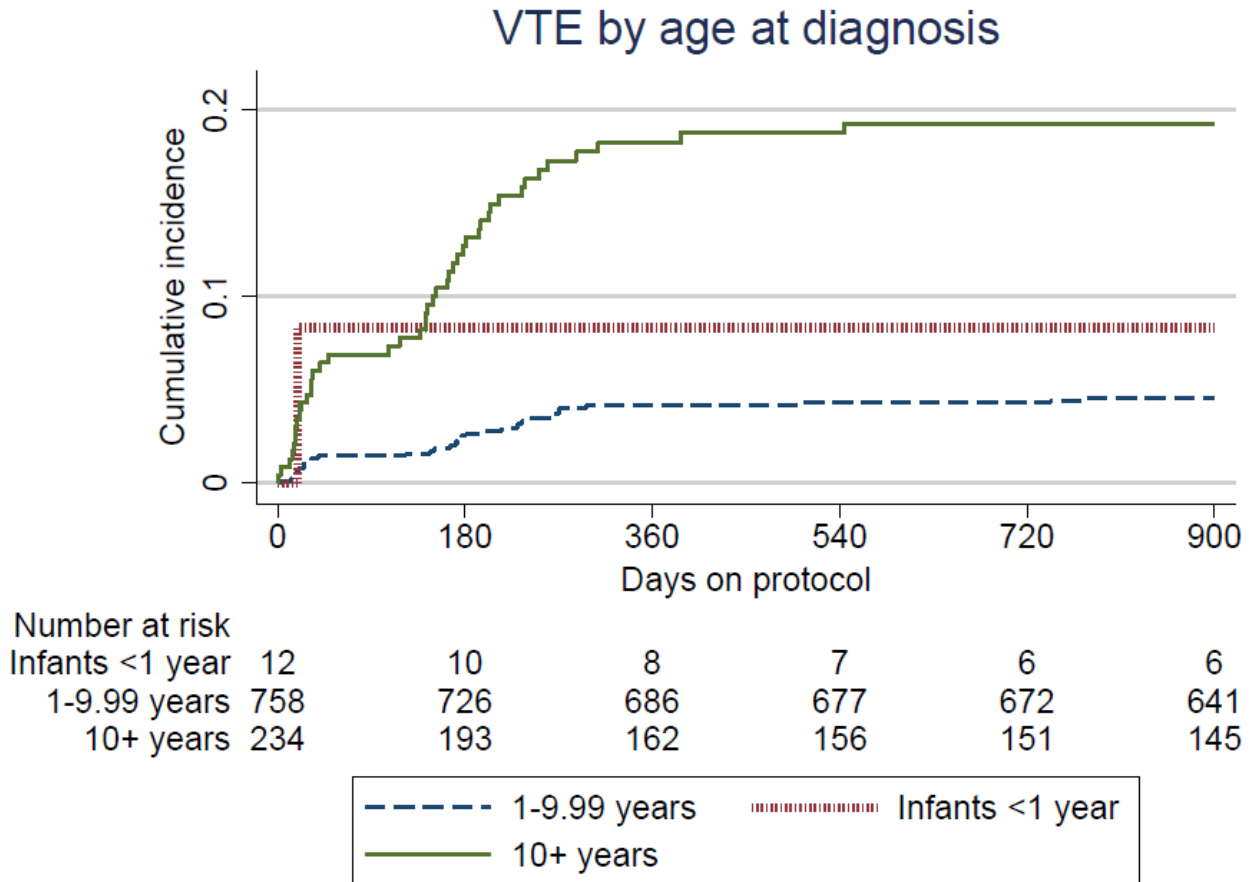
Supplemental Table 2: Association between rs2519093 genotype, blood group, and cumulative incidence of thrombosis

	rs2519093 genotype			Cumulative incidence thrombosis
	TT	CT	CC	
A	38 (4)	221 (30)	96 (4)	10.7%
AB	0	21 (3)	10	9.9%
B	0	0	99 (8)	8%
O	0	1	456 (24)	5.3%

Numbers indicate total patients and (cases of venous thrombosis). Cumulative incidence is for the occurrence of thrombosis by completion of therapy.

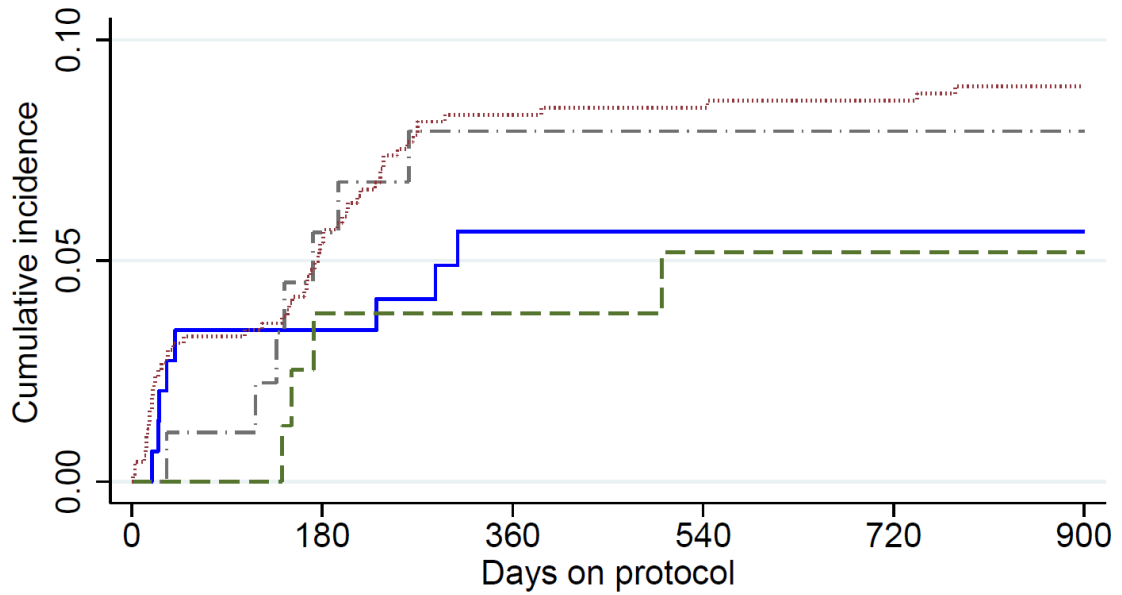
Supplemental Figure 1: Cumulative incidence of first venous thrombosis by age at diagnosis

Risk of venous thrombosis was significantly higher in those older than 10 years (HR 4.5, 95%CI 2.9-7.1, $p < 0.001$) compared to younger children but not in infants (HR 2.3, 95%CI 0.3-16.5, $p = 0.4$).



Supplemental Figure 2: Cumulative incidence of first venous thrombosis by genetic ancestry

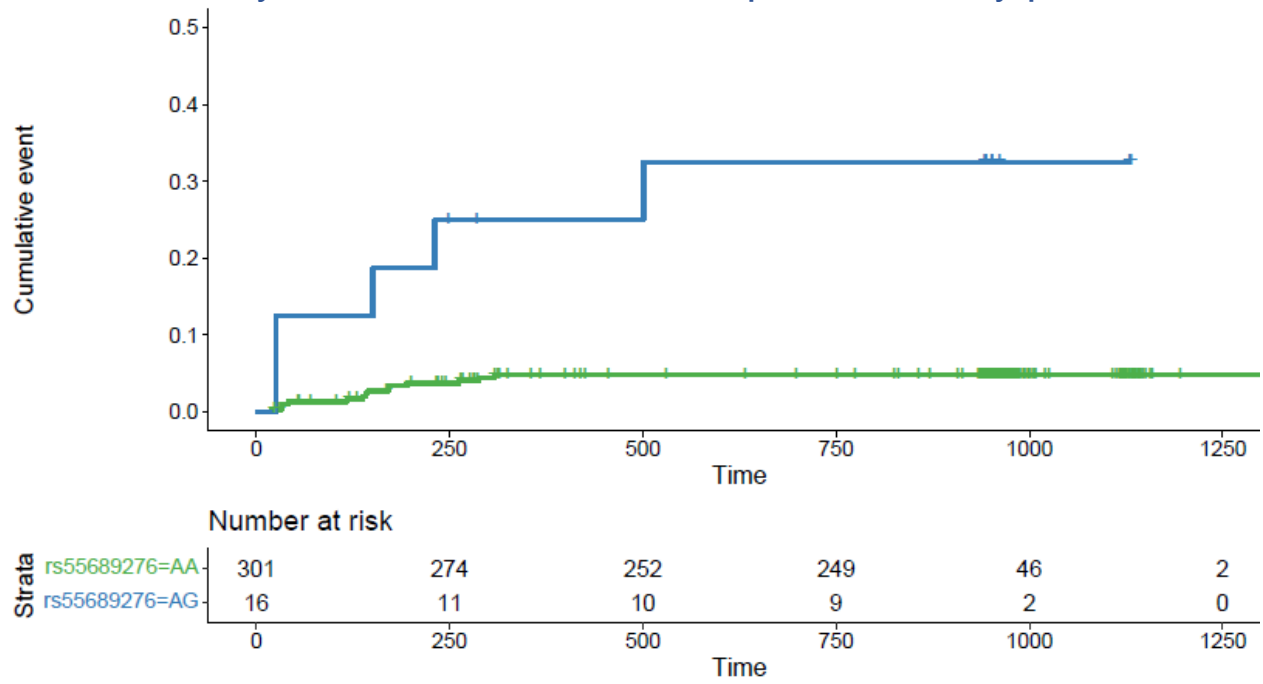
Rates of venous thrombosis during ALL therapy were similar across ancestral groups. Thrombosis occurred in 5.5% of African ancestry, 8.7% of Hispanic/ Native American ancestry, 8.8% of European ancestry, and 4.9% of other ancestry patients (p=0.4).



Number at risk	0	180	360	540	720	900
African	146	138	121	116	114	112
Hispanic	91	83	77	75	75	74
European	671	625	582	574	565	534
Other	81	75	70	69	69	66



Supplemental Figure 3: Cumulative incidence of first venous thrombosis by rs55689376 in non-European ancestry patients



Supplemental citations

1. Jeha S, Pei D, Choi J, et al. Improved CNS Control of Childhood Acute Lymphoblastic Leukemia Without Cranial Irradiation: St Jude Total Therapy Study 16. *J Clin Oncol*. 2019;37(35):3377-3391.
2. Pui CH, Campana D, Pei D, et al. Treating childhood acute lymphoblastic leukemia without cranial irradiation. *N Engl J Med*. 2009;360(26):2730-2741.
3. Das S, Forer L, Schonherr S, et al. Next-generation genotype imputation service and methods. *Nat Genet*. 2016;48(10):1284-1287.
4. Yang W, Wu G, Broeckel U, et al. Comparison of genome sequencing and clinical genotyping for pharmacogenes. *Clin Pharmacol Ther*. 2016;100(4):380-388.
5. Karol SE, Yang W, Van Driest SL, et al. Genetics of glucocorticoid-associated osteonecrosis in children with acute lymphoblastic leukemia. *Blood*. 2015;126(15):1770-1776.