Candidate gene association studies and risk of childhood acute lymphoblastic leukemia: a systematic review and meta-analysis

Jayaram Vijayakrishnan and Richard S. Houlston

Section of Cancer Genetics, Institute of Cancer Research, Sutton, Surrey, UK

Citation: Vijayakrishnan J and Houlston RS. Candidate gene association studies and risk of childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. Haematologica 2010;95(8):1405-1414. doi:10.3324/haematol.2010.022095

Online Supplementary Table S1. Studies of polymorphisms and risk of childhood acute lymphoblastic leukemia. Abbreviations: SD standard deviation; R: range; Yrs: years.

Reference	Place of study	Gene studied	Ethnicity	N	Cases	N	Controls
Gast A *et al*, 2007[1]	Germany	*MTR* *MTHFD1* *SHMT1* *RFC1* *TYMS* *MTRR*	Portuguese	460	460 childhood ALL cases, mean age 6.9 yrs (SD, 4.4); 273 male, 187 female. 269 c-ALL, 84 pre B-cell, 74 T-cell, 8 pre T-cell and 25 undefined cellular subtypes.	552	Population controls matched for ethnicity and geographic origin.
Krajinovic M *et al*, 1999[2]	Canada	*CYP1A1* *CYP2D6* *GSTM1* *GSTT1*	French-Canadian	177	110 males, 67 females, mean age 8yrs (+/-4.9); 137 pre-B-cell, 20 T-cell and 20 undetermined.	304	Population controls matched for age and geographic origin.
Krajinovic M *et al*, 2002[3]	Canada	*CYP2E1* *MPO* *NQO1*	French-Canadian	174	Childhood ALL, median age 5.2 yrs; 134 pre-B cell, 23 T-cell ALL, 17 undetermined lineage.	304	Controls from large institutional DNA data bank, matched for ethnicity and geographic origin.
Balta G *et al*, 2003[4]	Turkey	*CYP1A1* *GSTM1* *GSTT1* *GSTP1* *MTHFR*	Turkish	139	Childhood ALL cases, mean age 6.8 yrs(+/-4.1); 75 B-cell, 41non-B cell, 28 undetermined lineages.	185	Randomly selected, unrelated, healthy volunteers without any evidence of malignancy who are the brothers and sisters of the patients visiting the same hospital for mild illnesses.
Canalle R *et al*, 2004[5]	Brazil	*CYP1A1* *CYP2E1* *GSTM1* *GSTT1* *GSTP1*	Mixed	113	Childhood ALL. 73 males, 40 females, mean age 6.1yrs; 9 pro B -cell, 77 pre B-cell, 23 T-cell ALL, 4 undetermined. Ethnicity 98 white, 5 black and 10 mulattos.	221	Blood donor controls.159 males and 62 females, mean age 31.5, matched for ethnicity and geographic region.
Clavel J *et al*, 2005[6]	France	*CYP1A1* *GSTM1* *GSTP1* *GSTT1* *NQO1* *EPHX1*	Mixed	190	Childhood ALL, <15 yrs age; <7% non-Caucasian cases. Subtypes not defined.	105	Hospital patient controls recruited from orthopedic departments stratified by age, gender, hospital and ethnic origin.
Sayitoglu M *et al*, 2006[7]	Turkey	*CYP1A1* *CYP2D6* *CYP2D6* *CYP2E1* *GSTT1* *GSTM1*	Turkish	119	119 pediatric-ALL, mean age 7.8 yrs (+/-4.9). Subtypes not defined.	140	Turkish Caucasian members of faculty and hospital staff and students from the same geographic distribution as cases. Mean age 28.7, SD 8.3.

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Ulusoy G *et al*, 2007[8]	Turkey	*CYP2E1* *CYP2E1* *CYP2E1*	Turkish Caucasian	168	Childhood leukemia, 64 females, 104 males. Mean age 7.2, SD 3.8 years. Subtypes not specified.	207	Healthy unrelated Turkish volunteers (125 females, 82 males), mean age, 31.5 (SD 12yrs)
Lee KM *et al*, 2009[9]	Korea	*CYP1A1*	Korean	176	Childhood leukemia aged 0-18 yrs; subtypes not specified.	164	Hospital based controls aged 0-18 without history of childhood cancer, recruited through department of pediatrics, Seoul National University
Jamroziak K *et al*, 2004[10]	Poland	*MDR1*	Caucasian Slavic origin	113	Childhood ALL, subtypes not defined.	175	Caucasians of Slavic origin. Source not-specified.
Urayama K, *et al*, 2007[11]	USA	*MDR1*	Mixed	294	Childhood ALL <15 yrs at diagnosis; subtypes not defined.	369	Population-based, age, sex and ethnicity matched controls ascertained through birth certificate registration.
Hattori H *et al*, 2007[12]	Japan	*MDR1*	Japanese	140	Childhood ALL, mean age 6.1 years (R: 1.0-15.0) years; 105 common, 5 pre-B, 13 T-cell, 15 null, 4 mixed and 15 unspecified.	96	Unrelated, healthy Japanese children, mean age 7.7 years.
Semsei AF *et al*, 2007[13]	Hungary	*MDR1* *BCRP*	Hungarian Caucasian	383	Childhood ALL, mean age 6.1 yrs (SD 3.9); 291 B-cell, 53 T-cell.	189	Blood donors randomly chosen and matched for ethnicity and geographical region.
Leal-Ugarte E *et al*, 2008[14]	Mexico	*MDR1*	Mexican	107	Childhood ALL, mean age 7 yrs (1-14); 104 ALL-L1, 3 ALL-L2.	111	Healthy controls, recruitment details unspecified.
Eguchi-Ishimae M *et al*, 2005[15]	Japan	*NQO1*	Japanese	72	Infant ALL <18 months at diagnosis; 49 MLL (+) 23 MLL (-), subtypes not specified.	197	Cord blood samples.
Lanciotti M *et al*, 2005[16]	Italy	*NQO1*	Italian	156	Childhood ALL 18 MLL (-) infant age, 32 MLL (+) infant, resulting a 50 total infant ALL age < 12 months and 12 MLL(+) pediatric, 94 MLL(-), age <15 yrs. Cellular subtypes not specified.	147	Hospital based controls recruited from patients admitted for trauma, acute infection, or minor surgical procedure.
Kracht T *et al*, 2004[17]	Germany	*NQO1*	German	138	Childhood ALL, 35 MLL/AF4, median age 0.77 yrs; 31 BCR/ABL1, median age 8.33 yrs, 72 TEL/AML1. Cellular subtypes not specified.	190	Blood donors (16-68 years of age, 130 males and 60 females) with no history of malignant neoplastic disease.
Wiemels J *et al*, 1999[18]	UK	*NQO1*	Mixed	99	Childhood ALL, 36 MLL (+), 21 MLL/AF4, 50 TEL/AML (+) 29 hyperdipliod, age <15 yrs; cellular subtypes not specified.	100	Cord blood samples from healthy individuals.
Sirma S *et al*, 2004[19]	Turkey	*NQO1*	Turkish	189	Childhood ALL, median age 8 years (R: 1-16); Cellular subtypes not specified.	286	Normal population based controls with an age range of 2-60 years from different geographical areas of the country.
Chen C *et al*, 1997[20]	USA	*GSTM1* *GSTT1*	Black White	34 163	Childhood ALL with Cellular subtypes not described.	416	Population based control recruited from local blood donors, 213 white and 203 black.
Saadat I *et al*, 2000[21]	Iran	*GSTM1*	Iranian	38	Childhood ALL, mean age 8.2years (SD 2.6 yrs); 48 male, 27 females. Cellular subtypes not specified.	75	Healthy blood donors ranging in age from 3 to 13 years.
Davies S M *et al*, 2002[22]	USA	*GSTM1* *GSTT1*	Mixed	710	Childhood ALL, 616 white, 35 black, 35 Hispanic, 6 Asian and 18 mixed races; 463 B-cell, 95 T-cell, 1 null, 64 mixed, 87 undefined.	733	532 white non-Hispanic and 201 black individuals; blood donors and infant heel stick cards.
Krajinovic M *et al*, 2002[23]	Canada	*GSTP1*	French-Canadian white	278	Childhood ALL, mean age 4.9 yrs; 231 pre-B-cell, 29 T-cell ALL and 18 undetermined.	302	Healthy unrelated controls matched for ethnicity and geographic distribution.
Alves S *et al*, 2002[24]	North Portugal	*GSTT1* *GSTM1*	Portuguese	47	Childhood ALL, cellular subtypes not specified.	102	Healthy controls from same geographic area as cases.
Barnette P *et al*, 2004[25]	USA	*GSTM1* *GSTT1* *GSTP1* *GSTM3*	Mixed	189	Childhood ALL age < 18 yrs; cellular subtypes not specified.	340	Population based controls from the state of Utah -340 Guthrie cards of infants born in the year 2001-2002.
Pakakasama S *et al*, 2005[26]	Thailand	*GSTM1* *GSTT1* *CYP 1A1* *CYP 3A4* *CYP 3A5*	Thai	107	Childhood ALL, median age of 6 years, 3 months; 94 B-cell, 10 T-cell and 3 undetermined.	320	Healthy volunteers with no history of cancer, 165 males.
Pigullo S *et al*, 2007[27]	Italy	*GSTT1* *GSTM1* *GSTP1*	Caucasian	353	Childhood ALL aged <18 years; cellular subtypes undefined.	384	Hospital based controls with trauma or infection.

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Gatedee J *et al*, 2007[28]	Thailand	*GSTP1*	Thai	100	Childhood ALL, median age 5yrs (10months-14yrs 9months); 21 early pre B-cell, 55 Pre-B-cell, 1 B-cell and 13 T-cell.	100	Healthy Thai controls with normal blood counts.
Franco RF *et al*, 2001[29]	Brazil	*MTHFR*	64 White 6 Black 1 Mulatto	71	Childhood ALL, mean age 7.6 years (R: 2months - 15 yrs); 55 B-cell, 16 T-cell.	71	Controls matched for age, gender and race without evidence of malignancy. Ethnicity; 64 white, 6 black, 1 mulatto.
Wiemels JL *et al*, 2001[30]	UK	*MTHFR*	Mixed	253	Childhood ALL, age <15 yrs; <14% minority ethnicity, 37 MLL-rearranged, 78 TEL-AML1 (+), 138 hyper diploid cases. Cellular subtypes not defined.	200	Caucasian umbilical cord blood samples from unselected healthy new borns in UK.
Krajinovic M *et al*, 2004[31]	Canada	*MTHFR*	Caucasian	270	Childhood ALL, median age 4.9 yrs; 228 pre-B-cell, 31 T-cell, 11 with undetermined lineage.	300	Hospital based controls recruited from non-oncology departments.
Thirumaran R *et al*, 2005[32]	Germany	*MTHFR*	Caucasian	453	Childhood ALL, mean age 6.9 yrs (+/- 4.4); cellular subtypes not specified.	1448	Matched Caucasian controls.
Oliviera E *et al*, 2005[33]	Portugal	*MTHFR*	Caucasian	103	Pediatric ALL, aged < 16 yrs; cellular subtypes not specified.	111	Young volunteers born in the same geographic area.
Reddy H and Jamil K, 2005[34]	India	*MTHFR*	Asian	135	Childhood ALL, age 1-10years; cellular subtypes not specified.	142	Randomly selected children registered with the same institute as cases.
Schnakenberg E *et al*, 2005[35]	Germany	*MTHFR*	Caucasian	443	Pediatric ALL, aged < 18 yrs; 344 pre B-cell, 81 T-cell, 4 Biphenotypic, 14 unknown phenotype.	379	Blood donor controls.
Chatzidakis K *et al*, 2006[36]	Greece	*MTHFR*	Caucasian	52	Childhood ALL, age of 5.3 yrs (4months-13.4 yrs); 45 B-cell and 7 T-cell cases.	88	Adults with no history of malignancy.
Zanrosso C *et al*, 2006[37]	Brazil	*MTHFR*	Mixed	176	Mixed ethnicity childhood ALL, mean age of 6.2 years; 167 B-precursor 9 T-cell cases.	199	120 white, 79 non-white; unselected healthy subjects.
Giovannetti E *et al*, 2008[38]	Netherlands	*MTHFR* *TS*	Indonesian	71	71 pediatric leukemia mean age 6.1 yrs; cellular subtypes not specified.	44	44 Hospital based controls with 3-8 years of age.
Kamel A *et al*, 2007[39]	Egypt	*MTHFR*	Egyptian	88	88 pediatric ALL cases, median age of 6 years (range 1.5-18); precursor B-ALL cases.	311	Blood donors aged 18-48 years.
Alcasabas P *et al*, 2008[40]	Philippines	*MTHFR*	Filipino	189	Childhood ALL, median age 6.9 yrs (4months-18 yrs); cellular subtypes not defined.	394	Cord blood DNA from healthy infants.
de Jonge R *et al*, 2009[41]	Netherlands	*MTHFR* *SHMT1* *TS* *MTR* *RFC* *MTRR* *NNMT*	Caucasian	245	Pediatric ALL, aged < 18 yrs; 75% precursor B-cell and 25% T-cell.	500	Blood donor controls
Petra GB *et al*, 2007[42]	Slovenia	*MS* *TS* *MTRR* *MTHFR*	Caucasian	68	Childhood ALL, median age of 4.7 years; 51 B-cell, 8 T-cell and 9 undetermined.	258	Unrelated healthy Slovenian students, median age 24 years; without a history of malignancy.
Pakakasama S *et al*, 2007[43]	Thailand	*ERCC2* *XRCC1*	Thai	108	Childhood ALL, median age 6yrs and 3 months (R: 10months-14yrs 9months); cellular subtypes not specified.	317	Healthy volunteers.
Batar B *et al*, 2009[44]	Turkey	*ERCC2* *XRCC1*	Turkey	70	Childhood ALL, mean age of 5.9 yrs (SD, 3.66); 56 common-ALL, 5 pre-B - cell and 9 T-cell cell.	75	Randomly selected from healthy children with no history of cancer matched to the cases by age and sex.
Joseph T *et al*, 2004[45]	India	*CYP1A1* *CYP2D6* *GSTM1* *GSTT1*	Indian	118	Pediatric ALL cases comprising of 77 males; aged <15years; 99 L1, 18 L2, 1 L3 smear subtypes.	118	Out patient clinic based controls matched for age and sex.
Joseph T *et al*, 2005[46]	India	*XRCC1*	Indian	117	Childhood leukemia, aged <15years; cellular subtypes not specified.	117	Hospital based controls matched for age, sex and ethnicity.
Kim KN *et al*, 2006[47]	Korea	*MTHFR*	Korean	66	Childhood leukemia, mean age of 9.03 Yrs (R: 1-15); cellular subtypes not specified	100	Randomly selected; without neoplastic or thrombotic diseases

Online Supplementary Table S2. Summary of odds ratios of individual studies along with their confidence intervals.

		Heterozygous model				Homozygous model				Carrier status			
			Confidence intervals				Confidence intervals				Confidence intervals		
Study	Polymorphism	OR	Upper limit	Lower limit	*P*	OR	Upper limit	Lower limit	*P*	OR	Upper limit	Lower limit	*P*
Franco RF *et al.*[29]	*MTHFR*, C677T	0.48	0.98	0.23	0.04	0.28	0.85	0.09	0.02	0.42	0.84	0.21	0.01
Balta G *et al.*[4]	*MTHFR*, C677T	0.87	1.37	0.56	0.56	1.74	4.56	0.67	0.25	0.95	1.47	0.61	0.81
Krajinovic M *et al.*[31]	*MTHFR*, C677T	1.12	1.59	0.78	0.54	0.76	1.28	0.45	0.30	1.02	1.43	0.73	0.90
Thirumaran R *et al.*[32]	*MTHFR*, C677T	0.86	1.08	0.69	0.20	1.07	1.49	0.76	0.71	0.90	1.12	0.73	0.35
Reddy K *et al.*[34]	*MTHFR*, C677T	2.06	3.36	1.26	<0.01	2.17	7.20	0.65	0.20	2.07	3.34	1.28	<0.01
Schnakenberg E *et al.*[35]	*MTHFR*, C677T	1.25	1.67	0.93	0.14	1.03	1.63	0.65	0.90	1.20	1.58	0.91	0.19
Chatzidakis K *et al.*[36]	*MTHFR*, C677T	0.40	0.82	0.19	0.01	0.34	1.39	0.09	0.12	0.39	0.78	0.19	0.01
Zanrosso C *et al.*[37]	*MTHFR*, C677T	0.96	1.72	0.54	0.89	1.10	3.01	0.40	0.86	0.98	1.71	0.56	0.95
Zanrosso C *et al.*[37]	*MTHFR*, C677T	0.46	0.92	0.23	0.03	0.35	1.11	0.11	0.07	0.43	0.82	0.23	0.01
Petra GB *et al.*[42]	*MTHFR*, C677T	1.12	1.96	0.64	0.69	0.52	1.44	0.19	0.20	0.97	1.66	0.57	0.92
Giovanetti E *et al.*[38]	*MTHFR*, C677T	0.93	2.81	0.31	0.90	NA	NA	NA	0.22	1.19	3.46	0.41	0.75
Kamel A *et al.*[39]	*MTHFR*, C677T	1.24	2.04	0.76	0.38	1.40	3.55	0.55	0.48	1.26	2.03	0.79	0.33
Alcasabas P *et al.*[40]	*MTHFR*, C677T	1.38	2.13	0.89	0.15	1.11	4.50	0.27	0.88	1.36	2.07	0.89	0.16
Kim KN *et al.*[47]	*MTHFR*, C677T	0.98	2.05	0.46	0.95	0.74	1.93	0.28	0.54	0.91	1.86	0.44	0.80
de Jonge R *et al.*[41]	*MTHFR*, C677T	0.70	0.97	0.51	0.03	0.69	1.18	0.40	0.17	0.70	0.95	0.51	0.02
Wiemels J *et al.*[30]	*MTHFR*, C677T	1.05	1.59	0.69	0.83	0.77	1.38	0.43	0.37	0.97	1.42	0.66	0.86
Oliveira E *et al.*[33]	*MTHFR*, C677T	0.82	1.43	0.47	0.49	0.52	1.67	0.16	0.27	0.78	1.34	0.45	0.37
Franco RF *et al.*[29]	*MTHFR*, A1298C	1.22	2.41	0.62	0.57	2.85	15.58	0.52	0.21	1.33	2.58	0.69	0.40
Krajinovic M *et al.*[31]	*MTHFR*, A1298C	0.89	1.26	0.63	0.52	0.38	0.78	0.19	0.01	0.79	1.10	0.57	0.16
Thirumaran R *et al.*[32]	*MTHFR*, A1298C	1.01	1.26	0.81	0.94	1.16	1.66	0.82	0.40	1.04	1.29	0.84	0.73
Reddy K *et al.*[34]	*MTHFR*, A1298C	1.94	3.21	1.17	0.01	1.94	5.08	0.74	0.17	1.94	3.17	1.18	0.01
Schnakenberg E *et al.*[35]	*MTHFR*, A1298C	0.92	1.24	0.69	0.60	0.68	1.07	0.43	0.10	0.87	1.15	0.66	0.32
Zanrosso C *et al.*[37]	*MTHFR*, A1298C	0.90	1.60	0.51	0.73	1.13	3.34	0.38	0.82	0.94	1.62	0.54	0.81
Zanrosso C *et al.*[37]	*MTHFR*, A1298C	2.10	4.06	1.09	0.03	1.40	5.98	0.33	0.65	2.01	3.79	1.06	0.03
Petra GB *et al.*[42]	*MTHFR*, A1298C	1.58	2.80	0.89	0.12	1.34	3.14	0.58	0.49	1.52	2.62	0.88	0.13
Kamel A *et al.*[39]	*MTHFR*, A1298C	0.38	0.66	0.22	<0.01	0.67	1.55	0.29	0.35	0.43	0.71	0.26	<0.01
Alcasabas P *et al.*[40]	*MTHFR*, A1298C	1.51	2.24	1.02	0.04	1.94	3.24	1.16	0.01	1.61	2.34	1.11	0.01
de Jonge R *et al.*[41]	*MTHFR*, A1298C	0.98	1.36	0.70	0.89	1.62	2.66	0.99	0.06	1.09	1.48	0.80	0.59
Kim KN *et al.*[47]	*MTHFR*, A1298C	2.22	4.50	1.09	0.03	1.01	11.52	0.09	0.65	2.11	4.22	1.06	0.03
Wiemels J *et al.*[30]	*MTHFR*, A1298C	0.93	1.39	0.62	0.71	0.41	0.88	0.19	0.02	0.81	1.20	0.55	0.30
Oliveira E *et al.*[33]	*MTHFR*, A1298C	1.81	3.20	1.03	0.04	1.50	4.14	0.54	0.43	1.76	3.06	1.02	0.04
Petra G *et al.*[42]	*MTR* A2756G	0.62	1.15	0.33	0.12	0.21	1.63	0.03	0.10	0.55	1.01	0.30	0.05
Kamel A *et al.*[39]	*MTR* A2756G	1.05	1.76	0.63	0.84	0.71	2.53	0.20	0.59	1.01	1.65	0.61	0.98
Gast A *et al.*[1]	*MTR* A2756G	1.36	1.78	1.03	0.03	0.83	1.68	0.41	0.60	1.29	1.68	0.99	0.06
de Jonge R *et al.*[41]	*MTR* A2756G	1.13	1.59	0.81	0.47	1.57	3.81	0.65	0.31	1.17	1.62	0.84	0.35
Giovannetti E *et al.*[38]	*TS* 2R to 3R	1.22	35.40	0.04	0.62	0.45	11.30	0.02	0.39	0.53	13.25	0.02	0.43
Petra GB *et al.*[42]	*TS* 2R to 3R	1.23	2.34	0.64	0.54	1.46	3.12	0.68	0.33	1.30	2.39	0.70	0.41
de Jonge R *et al.*[41]	*TS* 2R to 3R	1.02	1.52	0.69	0.92	1.48	2.28	0.96	0.08	1.17	1.70	0.81	0.41
Gast A *et al.*[1]	*TS* 2R to 3R	0.95	1.31	0.68	0.74	1.06	1.53	0.74	0.75	0.98	1.34	0.72	0.92
de Jonge *et al.*[41]	*MTRR* A66G	0.82	1.21	0.55	0.31	0.74	1.14	0.48	0.17	0.79	1.13	0.55	0.20
Petra G *et al.*[42]	*MTRR* A66G	0.83	1.65	0.42	0.59	0.71	1.56	0.32	0.39	0.79	1.51	0.41	0.47
Gast A *et al.*[1]	*MTRR* A66G	0.71	0.99	0.52	0.04	0.63	0.90	0.43	0.01	0.68	0.93	0.50	0.01
de Jonge R *et al.*[41]	*SHMT1* C1420T	0.72	1.00	0.52	0.05	0.96	1.60	0.58	0.88	0.77	1.04	0.56	0.09
Gast A *et al.*[1]	*SHMT1* C1420T	0.84	1.10	0.65	0.21	1.34	2.09	0.85	0.20	0.92	1.18	0.72	0.51
de Jonge *et al.*[41]	*RFC1* G80A	1.34	1.91	0.94	0.10	2.06	3.25	1.31	<0.01	1.50	2.09	1.08	0.02
Gast *et al.*[1]	*RFC1* G80A	1.40	1.86	1.05	0.02	1.04	1.51	0.72	0.83	1.29	1.70	0.98	0.07
Clavel J *et al.*[6]	*NQO1*, C609T	1.00	1.67	0.59	0.99	1.86	6.98	0.49	0.35	1.07	1.76	0.65	0.80
Eguchi Ishimae M *et al.*[15]	*NQO1*, C609T	1.08	1.96	0.60	0.79	1.58	3.48	0.72	0.26	1.20	2.07	0.69	0.52
Krajinovic M *et al.*[3]	*NQO1*, C609T	1.54	2.30	1.04	0.03	1.16	2.98	0.45	0.77	1.49	2.19	1.02	0.04
Kracht T *et al.*[17]	*NQO1*, C609T	0.94	1.52	0.59	0.81	1.83	8.36	0.40	0.43	0.98	1.57	0.62	0.95
Wiemels J *et al.*[18]	*NQO1*, C609T	1.77	3.17	0.99	0.05	3.87	38.25	0.39	0.22	1.84	3.26	1.03	0.04
Sirma S *et al.*[19]	*NQO1*, C609T	0.74	1.08	0.50	0.12	0.66	1.99	0.22	0.46	0.73	1.07	0.51	0.10
Lanciotti M *et al.*[16]	*NQO1*, C609T	1.07	1.70	0.68	0.77	NA	NA	NA	NA	1.07	1.70	0.68	0.77

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Eguchi Ishimae M *et al.*[15]	*NQO1*, C465T	2.83	8.37	0.95	0.05	NA	NA	NA	NA	2.82	8.37	0.95	0.05
Krajinovic M *et al.*[3]	*NQO1*, C465T	1.41	2.53	0.79	0.25	NA	NA	NA	NA	1.36	2.44	0.76	0.29
Chen *et al.*[20]	*GSTT1* null allele	NA	NA	NA	NA	0.93	1.66	0.52	0.81	NA	NA	NA	NA
Chen *et al.*[20]	*GSTT1* null allele	NA	NA	NA	NA	1.71	3.71	0.79	0.17	NA	NA	NA	NA
Krajinovic M *et al.*[2]	*GSTT1* null allele	NA	NA	NA	NA	0.91	1.52	0.55	0.72	NA	NA	NA	NA
Davies S M *et al.*[22]	*GSTT1* null allele	NA	NA	NA	NA	0.94	1.3	0.69	0.71	NA	NA	NA	NA
Davies S M *et al.*[22]	*GSTT1* null allele	NA	NA	NA	NA	0.54	1.36	0.21	0.19	NA	NA	NA	NA
Alves S *et al.*[24]	*GSTT1* null allele	NA	NA	NA	NA	0.69	1.62	0.3	0.39	NA	NA	NA	NA
Balta *et al.*[4]	*GSTT1* null allele	NA	NA	NA	NA	0.9	1.53	0.53	0.70	NA	NA	NA	NA
Barnette *et al.*[25]	*GSTT1* null allele	NA	NA	NA	NA	0.44	0.93	0.21	0.03	NA	NA	NA	NA
Canalle *et al.*[5]	*GSTT1* null allele	NA	NA	NA	NA	1.18	2.05	0.67	0.56	NA	NA	NA	NA
Pakakasama *et al.*[26]	*GSTT1* null allele	NA	NA	NA	NA	1.42	2.21	0.92	0.12	NA	NA	NA	NA
Clavel *et al.*[6]	*GSTT1* null allele	NA	NA	NA	NA	1	1.79	0.57	0.99	NA	NA	NA	NA
Sayitoglu *et al.*[7]	*GSTT1* null allele	NA	NA	NA	NA	1.23	2.21	0.69	0.49	NA	NA	NA	NA
Pigullo *et al.*[27]	*GSTT1* null allele	NA	NA	NA	NA	0.72	1.09	0.48	0.12	NA	NA	NA	NA
Joseph *et al.*[45]	*GSTT1* null allele	NA	NA	NA	NA	1.82	4.16	0.8	0.16	NA	NA	NA	NA
Chen *et al.*[20]	*GSTM1* null allele	NA	NA	NA	NA	1.07	1.61	0.71	0.75	NA	NA	NA	NA
Chen *et al.*[20]	*GSTM1* null allele	NA	NA	NA	NA	1.84	3.89	0.87	0.11	NA	NA	NA	NA
Krajinovic M *et al.*[2]	*GSTM1* null allele	NA	NA	NA	NA	1.76	2.58	1.2	<0.01	NA	NA	NA	NA
Saadat I *et al.*[21]	*GSTM1* null allele	NA	NA	NA	NA	2.63	5.86	1.18	0.02	NA	NA	NA	NA
Davies S M *et al.*[22]	*GSTM1* null allele	NA	NA	NA	NA	1	1.26	0.79	0.99	NA	NA	NA	NA
Davies S M *et al.*[22]	*GSTM1* null allele	NA	NA	NA	NA	1.43	2.99	0.68	0.34	NA	NA	NA	NA
Alves *et al.*[24]	*GSTM1* null allele	NA	NA	NA	NA	2.22	4.58	1.07	0.03	NA	NA	NA	NA
Balta *et al.*[4]	*GSTM1* null allele	NA	NA	NA	NA	1.03	1.61	0.66	0.90	NA	NA	NA	NA
Barnette *et al.*[25]	*GSTM1* null allele	NA	NA	NA	NA	0.82	1.29	0.51	0.39	NA	NA	NA	NA
Canalle *et al.*[5]	*GSTM1* null allele	NA	NA	NA	NA	0.88	1.39	0.56	0.58	NA	NA	NA	NA
Pakakasama *et al.*[26]	*GSTM1* null allele	NA	NA	NA	NA	1.66	2.66	1.03	0.04	NA	NA	NA	NA
Clavel *et al.*[6]	*GSTM1* null allele	NA	NA	NA	NA	1.07	1.72	0.66	0.78	NA	NA	NA	NA
Sayitoglu *et al.*[7]	*GSTM1* null allele	NA	NA	NA	NA	1.56	2.58	0.94	0.08	NA	NA	NA	NA
Pigullo *et al.*[27]	*GSTM1* null allele	NA	NA	NA	NA	0.82	1.1	0.61	0.19	NA	NA	NA	NA
Joseph *et al.*[45]	*GSTM1* null allele	NA	NA	NA	NA	2.1	3.67	1.21	<0.01	NA	NA	NA	NA
Krajinovic M *et al.*[2]	*GSTP1* A1578G	1.33	1.88	0.94	0.10	0.96	1.72	0.54	0.90	1.26	1.74	0.90	0.17
Gatedee J *et al.*[28]	*GSTP1* A1578G	1.01	1.80	0.56	0.98	2.58	13.85	0.48	0.25	1.09	1.91	0.62	0.77
Canalle R *et al.*[5]	*GSTP1* A1578G	1.03	1.65	0.64	0.91	1.11	2.58	0.48	0.81	1.04	1.64	0.66	0.86
Clavel J *et al.*[6]	*GSTP1* A1578G	0.97	1.61	0.59	0.90	1.10	2.46	0.49	0.83	0.99	1.60	0.61	0.98
Pigullo M *et al.*[27]	*GSTP1* A1578G	1.10	1.51	0.80	0.55	1.18	2.00	0.69	0.55	1.11	1.50	0.83	0.47
Barnette P *et al.*[25]	*GSTP1* A1578G	0.90	1.51	0.53	0.69	0.97	2.15	0.44	0.94	0.91	1.49	0.56	0.72
Barnette P *et al.*[25]	*GSTP1* C2293T	0.92	1.87	0.45	0.81	NA	NA	NA	NA	0.89	1.83	0.44	0.76
Krajinovic M *et al.*[23]	*GSTP1* C2293T	0.69	1.19	0.40	0.18	NA	NA	NA	NA	0.66	1.13	0.38	0.12
Joseph T *et al.*[45]	*CYP1A1*, T6235C.	2.58	4.72	1.41	<0.01	6.22	29.71	1.30	0.01	2.88	5.13	1.62	<0.01
Krajinovic M *et al.*[2]	*CYP1A1*, T6235C.	1.87	3.17	1.10	0.02	0.96	10.72	0.09	0.98	1.82	3.05	1.08	0.02
Sayitoglu A *et al.*[7]	*CYP1A1*, T6235C.	1.74	3.05	1.00	0.05	0.34	3.06	0.04	0.31	1.58	2.71	0.92	0.10
Balta G *et al.*[4]	*CYP1A1*, T6235C.	1.37	2.40	0.78	0.28	0.21	1.72	0.02	0.11	1.17	2.02	0.68	0.56
Canalle R *et al.*[5]	*CYP1A1*, T6235C.	0.96	1.58	0.59	0.89	4.03	16.56	0.98	0.04	1.09	1.75	0.68	0.73
Clavel J *et al.*[6]	*CYP1A1*, T6235C.	0.75	1.35	0.42	0.34	NA	NA	NA	NA	0.82	1.46	0.46	0.49
Lee K-M *et al.*[9]	*CYP1A1*, T6235C.	1.25	2.16	0.72	0.43	0.62	1.36	0.28	0.23	1.06	1.78	0.63	0.84
Joseph T *et al.*[45]	*CYP1A1*, A4889G	2.18	4.10	1.16	0.01	4.28	16.11	1.14	0.02	2.46	4.43	1.36	<0.01
Krajinovic M *et al.*[2]	*CYP1A1*, A4889G	0.80	1.67	0.38	0.55	NA	NA	NA	NA	0.87	1.79	0.42	0.71
Lee K-M *et al.*[9]	*CYP1A1*, A4889G	0.85	1.42	0.51	0.54	0.94	2.79	0.32	0.92	0.86	1.42	0.52	0.56
Ulusoy G *et al.*[8]	*CYP2E1**5B	1.91	4.80	0.76	0.16	NA	NA	NA	NA	1.91	4.80	0.76	0.16
Canalle R *et al.*[5]	*CYP2E1**5B	1.21	2.46	0.60	0.59	NA	NA	NA	NA	1.16	2.34	0.58	0.68
Krajinovic M *et al.*[3]	*CYP2E1**5B	2.85	6.73	1.21	0.01	NA	NA	NA	NA	2.85	6.73	1.21	0.01
Sayitoglu A *et al.*[7]	*CYP2E1**5B	3.47	9.18	1.31	0.01	NA	NA	NA	NA	3.47	9.18	1.31	0.01
Krajinovic M *et al.*[2]	*CYP2D6**4	1.17	1.76	0.78	0.45	1.63	4.34	0.61	0.33	1.21	1.80	0.82	0.33
Joseph T *et al.*[45]	*CYP2D6**4	0.49	1.21	0.19	0.12	NA	NA	NA	NA	0.49	1.21	0.19	0.12
Sayitoglu A *et al.*[7]	*CYP2D6**4	1.04	1.83	0.59	0.90	2.42	13.56	0.43	0.30	1.11	1.92	0.64	0.70
Sayitoglu A *et al.*[7]	*CYP2D6**3	0.49	1.94	0.12	0.30	NA	NA	NA	NA	0.49	1.94	0.12	0.30
Krajinovic A *et al.*[2]	*CYP2D6**3	0.76	2.19	0.26	0.61	5.45	52.86	0.56	0.10	1.12	2.76	0.45	0.81
Hattori H *et al.*[12]	*MDR1* C3435T	1.11	2.02	0.61	0.72	2.97	6.91	1.28	0.01	1.45	2.53	0.83	0.19
Jamroziak K *et al.*[10]	*MDR1* C3435T	0.83	1.43	0.48	0.50	1.63	2.99	0.89	0.12	1.09	1.76	0.67	0.74
Semsei F *et al.*[13]	*MDR1* C3435T	1.32	2.03	0.86	0.20	1.42	2.27	0.88	0.15	1.36	2.02	0.91	0.13
Urayama K *et al.*[11]	*MDR1* C3435T	0.97	1.40	0.67	0.88	0.99	1.51	0.65	0.96	0.98	1.38	0.69	0.90
Leal-Ugarte *et al.*[14]	*MDR1* C3435T	0.92	1.98	0.42	0.83	0.54	1.27	0.23	0.16	0.77	1.62	0.37	0.50
Urayama K *et al.*[11]	*MDR1* G2677T/A	0.99	1.42	0.69	0.95	1.15	1.83	0.73	0.54	1.03	1.46	0.73	0.87
Jamroziak K *et al.*[10]	*MDR1* G2677T/A	1.11	1.71	0.72	0.64	0.82	1.32	0.51	0.42	0.99	1.48	0.66	0.96
Joseph T *et al.*[46]	*XRCC1* C26304T	1.72	3.20	0.92	0.09	2.36	8.15	0.69	0.16	1.82	3.25	1.02	0.04
Pakakasama S *et al.*[43]	*XRCC1* C26304T	0.73	1.15	0.47	0.18	0.22	0.96	0.05	0.03	0.67	1.04	0.43	0.07
Batar B *et al.*[44]	*XRCC1* C26304T	1.79	4.19	0.76	0.18	NA	NA	NA	NA	2.01	4.64	0.87	0.10
Pakakasama S *et al.*[43]	*XRCC1* G27466A	0.96	1.85	0.50	0.91	NA	NA	NA	NA	0.90	1.71	0.47	0.75
Joseph T *et al.*[46]	*XRCC1* G27466A	1.42	2.51	0.80	0.23	1.68	10.31	0.27	0.57	1.43	2.50	0.82	0.20
Joseph T *et al.*[46]	*XRCC1* G27466A	1.90	3.35	1.08	0.03	2.42	5.89	1.00	0.05	2.01	3.40	1.19	0.01
Pakakasama S *et al.*[43]	*XRCC1* G28152A	2.17	3.45	1.36	<0.01	2.24	5.37	0.94	0.06	2.18	3.42	1.39	<0.01
Batar B *et al.*[44]	*XRCC1* G28152A	1.00	2.07	0.48	1.00	0.64	1.77	0.23	0.39	0.90	1.80	0.45	0.77
Batar B *et al.*[44]	*ERCC2* G23591A	0.86	1.78	0.42	0.69	1.00	2.56	0.39	1.00	0.90	1.77	0.46	0.76
Pakakasama S *et al.*[43]	*ERCC2* G23591A	0.72	1.45	0.36	0.35	NA	NA	NA	NA	0.69	1.38	0.34	0.29
Pakakasama S *et al.*[43]	*ERCC2* A35931C	1.01	1.80	0.57	0.96	5.98	66.73	0.54	0.10	1.10	1.92	0.63	0.73
Batar B *et al.*[44]	*ERCC2* A35931C	0.98	2.01	0.48	0.95	0.88	2.31	0.33	0.79	0.95	1.87	0.48	0.89
B cell ALL only.													
Chatzidakis *et al.*[38]	*MTHFR* C677T	0.35	0.76	0.16	<0.01	0.12	1.02	0.01	0.05	0.32	0.67	0.15	<0.01
Kamel *et al.*[39]	*MTHFR* C677T	1.24	2.04	0.76	0.40	1.4	3.54	0.55	0.48	1.26	2.03	0.79	0.33
Balta *et al.*[4]	*GSTM1* null allele	NA	NA	NA	NA	2.28	4.15	1.25	<0.01	NA	NA	NA	NA
Davies *et al.*[22]	*GSTM1* null allele	NA	NA	NA	NA	0.7	0.86	0.56	<0.01	NA	NA	NA	NA
Balta *et al.*[4]	*GSTT1* null allele	NA	NA	NA	NA	1.34	2.48	0.72	0.35	NA	NA	NA	NA
Davies *et al.*[22]	*GSTT1* null allele	NA	NA	NA	NA	0.77	1.05	0.57	0.10	NA	NA	NA	NA

Online Supplementary Figure S1. Forest plot of odds ratios (ORs) of childhood acute lymphoblastic leukemia associated with polymorphic variants. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% confidence intervals. The diamond (and broken line) represents the summary ORs computed under a fixed effects model, with 95% confidence interval given by its width. The unbroken vertical line is at the null value (OR=1.0). *(see related file)*

Online Supplementary Figure S2. Forest plots of significant odds ratios (ORs) of childhood acute lymphoblastic leukemia associated with polymorphic variants. Boxes denote allelic OR point estimates, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% confidence intervals. The diamond (and broken line) represents the summary ORs computed under a fixed effects model, with 95% confidence interval given by its width. The unbroken vertical line is at the null value (OR=1.0). *(see related file)*

Online Supplementary Figure S3. Egger's plot showing publication bias in studies reviewed. Regression asymmetry graph plots of the standardized effect estimates, where standardized effect size is defined by odds ratio (OR) / standard error of the OR, and precision by 1 / standard error of the OR. Also shown is regression line and the confidence interval about the intercept. Failure of this confidence interval to include zero indicates asymmetry in the funnel plot and may give evidence of publication bias. *(see related file)*

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