Folate Metabolism and Risk of Childhood Acute Lymphoblastic Leukemia: A Genetic Pathway Analysis from the Childhood Cancer and Leukemia International Consortium

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ABSTRACT

Background: Prenatal folate supplementation has been consistently associated with a reduced risk of childhood acute lymphoblastic leukemia (ALL). Previous germline genetic studies examining the one carbon (folate) metabolism pathway were limited in sample size, scope, and population diversity and led to inconclusive results.

Methods: We evaluated whether ~2,900 single-nucleotide polymorphisms (SNP) within 46 candidate genes involved in the folate metabolism pathway influence the risk of childhood ALL, using genome-wide data from nine case-control studies in the Childhood Cancer and Leukemia International Consortium ($n = 9{,}058$ cases including 4,510 children of European ancestry, 3,018 Latinx, and 1,406 Asians, and 92,364 controls). Each study followed a standardized protocol for quality control and imputation of genome-wide data and summary statistics were meta-analyzed for all children combined and by major ancestry group using METAL software.

Results: None of the selected SNPs reached statistical significance, overall and for major ancestry groups (using adjusted Bonferroni P-value of 5×10^{-6} and less-stringent P-value of 3.5×10^{-5} accounting for the number of "independent" SNPs). None of the 10 top (nonsignificant) SNPs and corresponding genes overlapped across ancestry groups.

Conclusions: This large meta-analysis of original data does not reveal associations between many common genetic variants in the folate metabolism pathway and childhood ALL in various ancestry groups.

Impact: Genetic variants in the folate pathway alone do not appear to substantially influence childhood acute lymphoblastic leukemia risk. Other mechanisms such as gene–folate interaction, DNA methylation, or maternal genetic effects may explain the observed associations with self-reported prenatal folate intake.

Introduction

Leukemia is the most common cancer in children comprised primarily of acute lymphoblastic leukemia (ALL). One-carbon micronutrients such as folic acid play an essential role in the maintenance of genomic integrity and epigenetic control. Pooled analyses of original data from the Childhood Cancer and Leukemia International Consortium (CLIC) have shown that self-reported prenatal folate and vitamin supplementation reduces the risk of childhood ALL (1). However, germline genetic studies investigating the role of the one carbon (folate) metabolism and childhood ALL risk mostly in European populations have been limited in size and scope focusing on single genes such as *MTHFR*, *TS*, *MTR*, and *MTRR*, and generally yielding inconsistent results (2). We conducted a meta-analysis of CLIC genetic data to investigate

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Table 1. Participants by country/study and ancestry: CLIC.

Country[a]	Study name (period)	Overall	Cases	Controls
Australia	Aus-ALL (1998–2006)	1,550	358	1,192
France	ESCALE (2003–2004)[e]	1,983	441	1,542[b]
	ESTELLE (2010–2011)[e]	1,758	343	1,415[c]
Japan	TCCSG (1990–2011)	4,254	540	3,714
	JPLSG (2012–2018)	2,149	548	1,601
United States	ACCESS, Texas (2005–ongoing)[e]	6,965	658	6,307
	CCLS, California (1995–2009)	2,011	1,184	827
	CCRLP, California (1988–2011)	76,317	3,482	72,835[d]
	COG, US-wide (2000–2014)	4,435	1,504	2,931
Total				
All combined		101,422	9,058	92,364
Major ancestry groups				
European		74,521	4,510	70,011
Latinx		12,972	3,018	9,954
Asian		11,738	1,406	10,332

Abbreviations: CCLS, California Childhood Leukemia Study; CCRLP, California Childhood Cancer Record Linkage Project, which does not overlap with CCLS; COG, Children Oncology Group; JPLSG, Japanese Pediatric Leukemia/Lymphoma Study Group; TCCSG, Tokyo Children Cancer Study Group.
[a]Alphabetical order.
[b]Generic controls from the SU.VI.Max study, France.
[c]Generic controls from the MONALISA Lille study, France.
[d]Includes publicly available controls from the Wellcome Trust Case–Control Consortium and Resource for Genetic Epidemiology Research in Adult Health and Aging awarded to the Kaiser Permanente Research Program on Genes, Environment, and Health and the University of California San Francisco Institute for Human Genetics, United States.
[e]Estimated proportion of B-cell/T-cell for studies with available subtype information: ESCALE (84%/16%), ESTELLE (80%/20%), ACCESS (89%/11%).

the role of ~2,900 candidate single-nucleotide polymorphisms (SNP) in the folate metabolism pathway among diverse populations.

Materials and Methods

This study is based on genome-wide data from nine CLIC case-control studies in Europe, North America, Asia, and Oceania, including 9,058 childhood ALL cases and 92,364 study-specific and publicly available controls (**Table 1**). Each study was given standardized quality control (QC) guidelines for generating genome-wide data, as following: (i) pre-imputation QC (separately for cases and controls if genotyped separately) included filters for SNP call rate <98%, sample call-rate per person <95%, Hardy Weinberg Equilibrium $P < 10^{-5}$ in controls, minor allele frequency (MAF) < 0.01; genome-wide identity by descent > 0.20, and genome heterozygosity rate within 6sd of mean; (ii) for populations with multiple ancestries, principal component analysis (PCA) was performed with known ancestral populations to identify racial and ethnic groups (Europeans, Asians, Latinx, and Black individuals), and exclude population outliers; (iii) PCAs were generated on post QC data for adjustment in association analyses; (iv) missing data were imputed to HRC reference panel, and (v) post-imputation QC thresholds included MAF < 0.01 and $r^2 < 0.5$. Each study conducted their analyses independently, separately by race and ethnicity (if applicable) using SNPTEST or Plink2, adjusting for PC eigenvectors as appropriate. Prior to sharing summary statistics, each study was asked to assess for genomic inflation and adjust accordingly (lambda < 1.1 was considered sufficient). Summary results for each study, including snpID (chr:position), alleles, allele frequency, risk estimate, standard error, *P*-value, genome build, separately by race/ethnicity, were uploaded to a secure portal. Details on each study are published elsewhere (3–8).

We identified 46 genes in the folate metabolism pathway by curating biological pathways in Gene Ontology, Kyoto Encyclopedia of Genes and Genomes, gene set enrichment analysis/MSigDB (Broad Institute), USC Genome Browser, and Bioconductor (R) databases and by reviewing published literature (**Table 2**). Each selected gene was annotated from the Genome Assembly GRCh37/hg19 using the Bioconductor R package, and SNPs were extracted within 5 kb upstream and downstream from each gene location using UCSC genome table browser, leading to 7,979 candidate SNPs. Genome-wide meta-analyses were conducted using METAL software (version March 2011) for 9,058 ALL cases combined and for the major ancestry subgroups separately i.e., European ($n = 4{,}510$ cases), Latinx ($n =$

Table 2. Selected genes in the folate metabolism pathway.

AHCY	*DHFRL1*	*MPST*	*RTBDN*
ALDH1L1	*DPEP1*	*MTHFD1*	*SARDH*
ALDH1L2	*FOLH1*	*MTHFD1L*	*SHMT1*
AMT	*FOLR1*	*MTHFD2*	*SHMT2*
ATIC	*FOLR2*	*MTHFD2L*	*SLC19A1*
ATPIF1	*FOLR3*	*MTHFR*	*SLC19A2*
BHMT	*FPGS*	*MTHFS*	*SLC19A3*
C2orf83	*FTCD*	*MTR*	*SLC25A32*
CBS	*GART*	*MTRR*	*SLC46A1*
CPS1	*GCH1*	*MUT*	*TYMS*
CTH	*GGH*	*NOX4*	
DHFR	*LRP2*	*PIPOX*	

Table 3. Top 10 SNPs and corresponding genes, sorted by crude *P*-value of the meta-risk estimate for all subjects combined and by ancestry group: CLIC.

Rs#	Symbol	Gene	Reference allele frequency	Beta coefficient	*P*-value
Total					
rs2239910	*SLC46A1*	Solute carrier family 46 (folate transporter), member 1/sterile alpha and TIR motif containing 1	0.3643	0.0788	2.65E−04
rs9371202	*MTHFD1L*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	0.8455	0.1103	4.35E−04
rs12947270	*SLC46A1*	Solute carrier family 46 (folate transporter), member 1/H3 histone, family 3B (H3.3B) pseudogene 2	0.675	−0.0781	5.28E−04
rs9322291	*MTHFD1L*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	0.865	0.1397	6.31E−04
rs34449727	*CPS1*	Carbamoyl-phosphate synthase 1, mitochondrial	0.3292	−0.078	7.61E−04
rs11679391	*SLC19A3*	Solute carrier family 19 member 3	0.3726	0.0777	8.36E−04
rs2268369	*LRP2*	Low-density lipoprotein receptor-related protein 2	0.5444	−0.0645	1.09E−03
rs2268367	*LRP2*	Low-density lipoprotein receptor-related protein 2	0.5445	−0.0643	1.12E−03
rs11886318	*LRP2*	Low-density lipoprotein receptor-related protein 2	0.5349	−0.0635	1.34E−03
rs28785011	*MTHFD1L*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	0.8654	0.1345	1.40E−03
European					
rs11679391	*SLC19A3*	Solute carrier family 19 (thiamine transporter), member 3	0.4029	0.1107	3.55E−04
rs9371202	*MTHFD1L*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	0.8636	0.1576	5.33E−04
rs2138406	*C2orf83*	Chromosome 2 open reading frame 83	0.1873	0.1185	1.21E−03
rs7601819	*SLC19A3*	Solute carrier family 19 (thiamine transporter), member 3	0.8777	0.1626	1.24E−03
rs7583413	*C2orf83*	Chromosome 2 open reading frame 83	0.8086	−0.1156	1.32E−03
rs76758508	*SHMT2*	Serine hydroxymethyltransferase 2	0.315	0.0958	1.63E−03
rs68176600	*NXPH4*	Neurexophilin 4	0.6767	−0.0949	1.69E−03
rs11679339	*SLC19A3*	Solute carrier family 19 (thiamine transporter), member 3	0.7727	−0.1108	1.74E−03
rs4973234	*SLC19A3*	Solute carrier family 19 (thiamine transporter), member 3	0.7727	−0.1093	1.96E−03
rs803456	*MTHFD1L*	Methylenetetrahydrofolate dehydrogenase (NADP+ dependent) 1-like	0.5117	0.0907	2.24E−03
Latinx					
rs8018688	*GCH1*	GTP cyclohydrolase 1	0.7902	0.1384	1.38E−03
rs9980564	*CBS*	cystathionine-beta-synthase	0.6155	0.1202	1.60E−03
rs7147201	*GCH1*	GTP cyclohydrolase 1	0.7875	0.1298	2.73E−03
rs9671455	*GCH1*	GTP cyclohydrolase 1	0.7462	0.1212	2.78E−03
rs56213135	*GCH1*	GTP cyclohydrolase 1	0.2014	−0.1308	2.79E−03
rs3759664	*GCH1*	GTP cyclohydrolase 1	0.1988	−0.13	3.07E−03
rs11886318	*LRP2*	Low density lipoprotein receptor-related protein 2	0.5423	−0.1056	3.24E−03
rs6433109	*LRP2*	Low density lipoprotein receptor-related protein 2	0.5391	−0.1047	3.37E−03
rs7600336	*LRP2*	Low density lipoprotein receptor-related protein 3	0.4182	0.1047	3.73E−03
rs113100590	*GCH1*	GTP cyclohydrolase 1	0.8052	0.1302	3.74E−03
Asian					
rs11018581	*NOX4*	NADPH oxidase 4	0.2848	0.2081	7.74E−05
rs11821838	*NOX4*	NADPH oxidase 4	0.2103	0.196	7.09E−04
rs6677781	*CTH*	Cystathionase	0.2337	0.1782	1.43E−03
rs7925419	*FOLH1*	Folate hydrolase 1	0.4587	0.1463	3.79E−03
rs609054	*FOLH1*	Folate hydrolase 2	0.5818	0.135	6.76E−03
rs2734002	*FOLH1*	Folate hydrolase 3	0.5818	0.1348	6.82E−03
rs10839236	*FOLH1*	Folate hydrolase 4	0.5658	0.1326	8.20E−03
rs3872578	*FOLH1*	Folate hydrolase 5	0.5659	0.1326	8.22E−03
rs9651571	*FOLH1*	Folate hydrolase 6	0.5658	0.1325	8.27E−03
rs7120943	*FOLH1*	Folate hydrolase 7	0.4342	−0.1321	8.44E−03

3,018 cases), and Asian ($n = 1{,}406$ cases). SNPs were included in the meta-analysis if (i) they were available in at least two studies and among >50,000 subjects overall or of European ancestry and >10,000 subjects of Asian or Latinx ancestry, and (ii) the allele frequency difference across studies was <0.5 among controls (as a quality control check), resulting in ~2,900 SNPs available for analysis [total and European ($n = 2{,}855$), Latinx ($n = 2{,}930$), Asian (n = 2,230)]. To account for multiple testing, we applied Bonferroni correction (adjusted *P*-value $= 5 \times 10^{-6}$) and a less-stringent correction defined by the number of "independent" SNPs (based upon 1,000 Genomes, calculating the pairwise genotypic correlation using a 100-SNP window, a 10-SNP shift, and a r^2 threshold of 0.2, which average to 350 independent SNPs) and the number of test for each four group examined (total, and Europeans, Latinx, and Asian ancestries) resulting in an adjusted *P*-value of 3.5×10^{-5} (0.05/350/4).

The study was approved by Institutional Review Boards for the California Health and Human Services and the University of California, Berkeley, and was conducted according to the U.S Common Rule.

Data availability

Only summary statistics were shared by participating studies and no new data were generated as part of this analysis. Original study-specific data may be available at the discretion of the individual study principal investigators (information may be requested from the corresponding author).

Results

None of the selected SNPs in the folate metabolism pathway reached the levels of significance defined above, overall and for the three major ancestry groups. **Table 3** presents the top 10 SNPs for all groups combined and by ancestry, with crude *P*-values. None of the 10 top SNPs (and corresponding genes) in each ancestry group overlapped (i.e., *C2orf83, MTHFD1L, NXPH4, SHMT2*, and *SLC19A3* in Europeans; *CBS, GCH1*, and *LRP2* in Latinx; and *CTH, FOLH1*, and *NOX4* in Asians).

Discussion

This CLIC study is the largest and most comprehensive to date to investigate the role of genetic variants in the folate metabolism pathway and childhood ALL risk among populations of diverse ancestries. We did not observe statistically significant associations with ~2,900 SNPs. Inherited genetic variants in the folate pathway alone do not appear to substantially influence childhood ALL risk. Alternatively, gene–folate interaction, epigenetic mechanisms, or maternal genetic effects may contribute to the risk.

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Authors' Contributions

C. Metayer: Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, writing–original draft, project administration, writing–review and editing. **L.G. Spector:** Resources, writing–review and editing. **M.E. Scheurer:** resources, writing–review and editing. **S. Jeon:** Formal analysis, writing–review and editing. **R.J. Scott:** Resources, writing–review and editing. **M. Takagi:** Resources, writing–review and editing. **J. Clavel:** Resources, writing–review and editing. **A. Manabe:** Resources, writing–review and editing. **X. Ma:** Resources, writing–review and editing. **E.M. Hailu:** Data curation, writing–review and editing. **P.J. Lupo:** Resources, writing–review and editing. **K.Y. Urayama:** Resources, writing–review and editing. **A. Bonaventure:** Resources, writing–review and editing. **M. Kato:** Resources, writing–review and editing. **A. Meirhaeghe:** Resources, writing–review and editing. **C.W. Chiang:** Formal analysis, writing–review and editing. **L.M. Morimoto:** Data curation, formal analysis, writing–original draft, writing–review and editing. **J.L. Wiemels:** Resources, formal analysis, writing–review and editing.

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