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Influences of Genetic Abnormality on the Risk of Acute Lymphoblastic Leukemia

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Abstract

Recent studies have provided evidence that common genetic variations could account for a proportion of leukemia in adult or children. To evaluate the contribution of candidate gene association studies to the understanding of genetic susceptibility to acute lymphoblastic leukemia we conducted a systematic review from published studies. The polymorphisms of genes encoding carcinogen-metabolizing enzymes (CYP family, NQO1, GST), enzymes involved in folate metabolism (MTHFR, MTRR, SHMT, TS), and DNA repair enzymes (RAD51, XRCC1, ERCC2), chromosome translocation and epigenetic events discussed in this review, can be introduced as candidate alterations in acute lymphoblastic leukemia.

Keyword: Acute lymphoblastic leukemia, genetic predisposition to disease, DNA repair enzymes, translocation, review.

Introduction

A single nucleotide polymorphism (SNP) is a source variance in a genome. A SNP ("snip") is a single base mutation of DNA. SNPs are the most simple form and most common source of genetic polymorphism in the human genome [1].

SNP related functional proteomics involve the identification of functional SNPs that modify proteins and protein active sites structure and function. Functional proteomics is closely tied to modern (post-genomic) drug design, and functional SNP information helps to discover new therapeutic targets [2]. Most interestingly, by developing a database of the modifications generated by functional (coding) SNPs in disease related proteins, new compounds can be made for correcting or enhancing the effects of those mutations in the population [3].

Acute lymphoblastic leukemia (ALL) is a malignant disease resulting from the accumulation of genetic alterations of B or T lymphoid precursor cells [4] and characterized by the malignant clonal proliferation of lymphoid cells that are blocked at an early stage of differentiation. ALL is the most common leukemia in children and accounts for 20% of acute leukemias in adults. The 5-year event-free survival is over 80% for children but only approximately 40% for adults with ALL [5]. Some factors have been introduced for ALL detection. These factors include clinical characteristics [gender, initial white blood cell count (WBC) and age at diagnosis], immunological features (leukemic immunophenotype), and somatic features (non-random recurrent chromosomal aberrations such as the Philadelphia chromosome), as well as germline genetic characteristics, which are assessable at diagnosis [6-8].

The environmental toxicants to which an individual is exposed are biotransformed and eliminated from the body after metabolic conversion mediated by Phase I and Phase II xenobiotic-metabolizing enzymes [9]. Phase I enzymes catalyze hydroxylation, reduction and oxidation reactions of xenobiotics (carcinogens/ drugs), often converting them into more active or toxic compounds [10]. Phase II enzymes catalyze conjugation reactions (glucuronidation, acetylation, methylation), thereby converting the metabolites into non-reactive, water-soluble products that are eliminated from the organism [11]. The genetic polymorphism underlying the variation in enzyme activity can modify susceptibility to diverse cancers, probably by influencing the activation and removal

of toxicants [12].

Here we present a review to present a good model for studies that want to investigate the genetic abnormality and find a probable pathway for increased risk to ALL.

Genetic

Gene mutations

Carcinogen metabolism genes

Metabolic gene variants that have been investigated as risk factors for ALL include polymorphisms in NQO1 (NADPH: quinone oxidoreductase) a cytosolic enzyme catalyzing reduction of quinones and prevention of their participation in redox cycling and thus in oxidative stress [13, 14]. Moreover, this protein was shown to interact with and stabilize the tumor suppressor protein p53 [15, 16]. NQO1 is expressed in most tissues including the bone marrow, where expression is thought to be highly inducible by xenobiotic with quinone moieties, and is up regulated during times of oxidative or electrophonic stress [17]. NQO1 can contribute to the formation of reactive oxidation species via oxidative cycling and therefore can act as a pro-oxidant [18].

Cytochrome P450 (CYP) 1A1 is a key enzyme in phase I bioactivation of xenobiotics and its polymorphism is associated with elevated enzymatic activity [19]. The P450 cytochrome system (CYP450) is a group of enzymes involved in steroid hormone biosynthesis as well as in metabolic activation of carcinogens [20]. genetic variants of enzymes which are involved in the oxidation activation and subsequent conjugation detoxification of carcinogens, such as PAHs and aromatic amines, may also play a role in susceptibility to leukemogenesis [21, 22].

Another member of carcinogen metabolism genes are glutathione S-transferases, a family of phase-II enzymes responsible for the detoxification of mutagenic electrophiles including polyaromatic hydrocarbons (PAHs) [23]. Glutathione S-transferase (GST) gene is one of the potential candidate genes to increase the risk of leukemia because it plays a significant role in Cadmium (a carcinogen) biotransformation and detoxification [24]. The principal function of GST enzymes is conjugation of hydrophobic and electrophilic compounds with reduced glutathione. The intracellular binding reaction with GSH is catalyzed by the GSTs and leads to stable GSH-metal conjugates being transported out of the cell and excreted via feces and urine [25]. Seven GSTs gene families (Alpha, Mu, Pi, Theta, Sigma, Omega, and Zeta) have been described and genetic polymorphisms have been reported for GSTM1, GSTP1, and GSTT1, resulting in altered enzyme activity [26, 27]. GSTT1 and GSTM1 are particularly important, because they have a deletion polymorphism resulting in impaired catalytic activity, which is associated with greater sensitivity to toxic compounds. The homozygous deleted (null genotype) of GSTT1 and GSTM1 genotypes have been associated with the loss of the enzyme activity and enhanced genotoxicity, and are believed to be key factors in determining susceptibility to diseases associated with exposure to xenobiotics such as leukemia [28] .

The human multidrug resistance 1 (MDR1) gene encodes P-glycoprotein, a membrane transport protein that extrudes a wide variety of lipophilic compounds, including xenobiotic and cellular metabolites [29]. P-glycoprotein uses an ATP-dependent efflux transport mechanism to minimize the exposure of potentially toxic compounds to the intracellular environment [30]. Interestingly, MDR1 is also highly expressed in several subclasses of bone marrow and peripheral leukocytes [31]. There is evidence demonstrating the involvement of P-glycoprotein in the release of interleukin-2, interleukin-4, and IFN-γ from lymphocytes [32].. Accordingly, P-glycoprotein could serve a role in leukemia etiology based on its transport of xenobiotics or modulation of immune function.

Folate metabolism genes

Dysfunctional folate metabolism is an attractive candidate in the etiology of ALL [33]. Folate levels along with genetic regulation of folate metabolism have been the focus of many investigations [34-37], predicated on the notion that they may influence the creation and/or expansion of the preleukemic clone via DNA hypomethylation of key regulator γ genes as well as uracil misincorporation into DNA, leading to double-strand breaks and chromosomal aberrations [38, 39]. Central to folate metabolism are the enzymes 5,10-methylenetetrahydrofolate reductase (MTHFR;), methionine synthase (MTR) and methionine synthase reductase (MTRR;). variants in These genes may impact on ALL risk through affecting folate metabolism [40-43]. Serine

hydroxyl methyltransferase (SHMT), thymidylate synthase (TS) and reduced folate carrier 1 (RFC1, a Folate transport), has also been proposed as risk factors for ALL [37, 44, 45].

A critical component of the folate metabolic pathway is methylenetetrahydrofolate reductase (MTHFR), which controls the balance between DNA methylation and synthesis via the irreversible conversion of 5,10-methylenetetrahydrofolate (5,10-MeTHF), required for DNA synthesis, to 5-methyltetrahydrofolate (5-MeTHF), a methyl donor for conversion of homocysteine to S-adenosylmethionine (SAM). Two common polymorphisms in MTHFR (677 C>T and 1298 A>C) result in decreased catalytic activity [46, 47]. Methionine synthase is a vitamin B12-dependent enzyme, which catalyzes the remethylation of homocysteine to methionine and the concurrent demethylation of 5-methyltetrahydrofolate to tetrahydrofolate. Methionine synthase has a key role in maintaining adequate intracellular folate, methionine and normal homocysteine concentrations. Methionine is an essential amino acid and precursor of S-adenosylmethionine, which is a universal methyl-group donor involved in methylation reactions including DNA methylation[48]. Polymorphism in methionine synthase (MTR) gene was initially thought to be associated with lower enzyme activity causing homocysteine elevation, DNA hypomethylation, CpG island and hypermethylation in tumor suppressor genes[49]. SHMT1 SNPs reduce the circulating folate levels, thus shunting 5,10-MeTHF toward DNA synthesis[50]. Another important enzyme in folate metabolism is thymidylate s ynthetase, a crucial factor in the synthesis of dTMP (2 ′-deoxythymidine-5 ′-monophosphate) in dividing cells that inhibition of either leads to "thymineless death". Thus TS represents an attractive target for developing antitumor agents, since genetic variant in this gene causes decreased enzyme activity, which is related to cancer [51].

DNA repair genes

Leukemia commonly arises as a result of DNA translocation, inversion or deletion in genes regulating lymphocyte development. Formation of translocations in leukemia are thought to involve DNA double-strand break formation by means other than aberrant V(D)J recombinase activity[53]. ALL is characterized by specific chromosomal abnormalities, such as translocations and changes in ploidy, that may result from unrepaired DNA damage such as double-strand breaks (DSBs) [33].

Alterations in innate DNA repair, cell cycle, or genomic maintenance processes may play a role in leukemia development [54] ,therefore DNA repair gene variants have been introduced as risk factors for ALL [55, 56]. SNPs in RAD51 gene, a protein

essential for homologous recombination and DNA repair, have been reported as risk factor in increased risk to ALL [57]. XRCC1 (X-Ray repair-cross complementing group 1) play a role in DNA single strand repair by forming protein complexes with DNA repair associated proteins [58]. There have been a number of studies on the association between XRCC1 polymorphisms and the risk of ALL [59-64]. Polymorphic variants in other DNA repair genes, including ERCC2 (excision repair-complementing group 2) have also been evaluated as risk factors for ALL for similar reasons [65]. BRCA2 plays a key role in the maintenance of genomic integrity, particularly through regulation of DNA repair by homologous recombination repair (HR)[66], a process that is also controlled by another tumor suppressor protein, BRCA1. HR is a largely an error-free process that restores the original sequence at the site of a DNA double-strand breaks (DSBs)[67].

Chromosome translocation

The development of ALL involves chromosomal changes including translocations causing fusion genes, as well as hyperdiploidy containing more than 50 chromosomes [4]. MLL rearrangements including t(4;11), t(11;19) and t(9;11) translocations are found in 8–13% of both adult and pediatric B-ALLs [68]. The most common alterations above 1 Mb have been reported as deletion 6q , 12p and 9p and duplication 4q and Xq [69]. The t(1;19) translocation in pediatric pre-B-cell acute lymphoblastic leukemia (ALL) fuses the genes, which encode the transcriptional activator E2A and homeobox pre-B-cell leukemia transcription factor 1 (PBX1), resulting in expression of the chimeric transcription factor E2A-PBX1. E2A-PBX1 can promote cell transformation both in vitro and in vivo [70]. The rare translocation t(8;14)(q11.2;q32) has been described in patients with B-cell acute lymphoblastic leukemia (ALL) [71]. The most significant structural chromosomal changes include: the poor-

risk abnormalities; t(9;22) (q34;q11), giving rise to the BCR/ABL fusion and rearrangements of the MLL gene; abnormalities previously designated as poor-risk; t(1;19) (q23;p13), producing the E2A/PBX1 and rearrangements of MYC with the immunoglobulin genes; and the probable good risk translocation t(12;21) (p13;q22), which results in the ETV6/AML1 fusion (72). These abnormalities occur most frequently in B-lineage leukemias, while rearrangements of the T cell receptor genes are associated with T-lineage ALL. Abnormalities of the short arm of chromosome 9, in particular homozygous deletions involving the tumor suppressor gene (TSG) p16(INK4A), are associated with a poor outcome [73]. Numerical chromosomal abnormalities are of particular importance in relation to prognosis. High hyperdiploidy (51-65 chromosomes) is associated with a good risk, whereas the outlook for patients with near haploidy (23-29 chromosomes) is extremely poor [74].

Epigenetic

Abnormalities in the epigenetic regulation of chromatin structure and function can lead to aberrant gene expression [75]. Chromatin remodeling is an important mechanism of epigenetic gene dysregulation in human cancers [76]. The epigenetic mechanisms currently believed to play a role in cancer include:

1) DNA methylation of cytosine bases in CG rich sequences, called CpG Islands; 2) post-translational modifications of histones, which are proteins that form the nucleosomes, which regulate the packaging structure of the DNA (called chromatin); 3) micro RNAs and non coding RNAs; and 4) nucleosome positioning [77].

Aberrant methylation of tumor suppressor genes is observed frequently in human malignancies, including acute leukemias [78]. Aberrant epigenetic lesions, in particular DNA methylation of promoter associated CpG islands, are common in acute lymphocytic leukemia (ALL) [79]. Hypermethylation of EPHA2 , -A4, -A5, -A6, -A7, -A10, EPHB1, -B2, -B3, -B4, EFNA1, -A3, -A5, and EFNB1 a nd -B2 genes have been detected in leukemia cell lines and primary ALL bone marrow samples [80]. The role of aberrant epigenetic modifications in cancer development and particularly in hematological malignancies such as acute leukemias has clearly been recognized [81]. It has been found that 154 genes are methylated in ALL patients. Interestingly, the expression of 13 genes implicated in the TP53 pathway is downregulated by hypermethylation[82]. Expression of ASPP1 is significantly reduced in ALL and is dependent on hypermethylation of the ASPP1 gene promoter. Abnormal ASPP1 expression is associated with abnormal function of the tumor-suppressor gene TP53 in ALL [83]. DNA methylation of promoter-associated CpG islands in estrogen receptor (ER), multidrug resistance gene 1 (MDR1), p73, p15, and p16 genes is the epigenetic DNA modification observed in acute leukemias [84]. It has been reported PPP2R3A (protein phosphatase 2, regulatory subunit B", alpha) is frequently methylated in T and B-ALL. While FBLN2 (fibulin 2) and THRB (thyroid hormone receptor, beta)

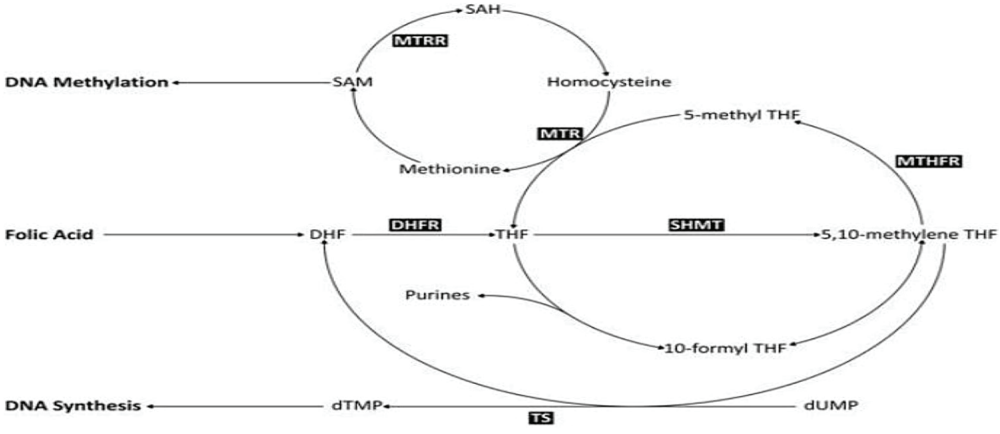

Figure 1: Metabolic folate pathway.

show frequent methylation in B-ALL, but are less frequently methylated in T-ALL[85]. A recent large-scale genome-wide study to identify genes methylated in adult ALL employing different high throughput approaches validated 15 genes as showing frequent methylation in ALL (GIPC2, RSPO1, MAGI1, CAST1, ADCY5, HSPA4L, OCLN, EFNA5, MSX2, GFPT2, GNA14, SALL1, MYO5B, ZNF382, MN1) (79). The post-translational modification of the core histones is critical to the regulation of chromatin structure that influence gene transcription [86]. Also, histone modifications contribute to the dysregulation of miRNAs in acute lymphoblastic leukemia (ALL) [87].

Conclusion

Genetic alteration in ALL has been extensively

Table1: Polymorphism of genes as risk factor for acute lymphoblastic leukemia.

Class/Gene	Polymorphism	Effect
Carcinogen metabolism		
CYP1A1	CYP1A1*2A,T6235C (rs4646903) CYP1A1*2B/*2C, A4889G (rs1048943)	Increased enzymatic activity
CYP2D6	CYP2D6*4, G1934A (rs3892097) CYP2D6*3, del2637 (rs35742686)	Abnormal splicing Premature termination
CYP2E1	CYP2E1*5B, G-1293C/C-1053T, (rs3813867/ rs2031920)	Altered expression in vitro
GSTT1	Deletion	Absent activity
GSTM1	Deletion	Absent activity
GSTP1	A1578G (rs1695)	Altered activity
NQO1	C609T (rs1800566), C465T (rs1131341)	Abolishes activity Alters mRNA splice site
MDR1	C3435T (rs1045642) G2677T/A (rs2032582)	Lower expression Altered activity
Folic acid pathway		
MTHFR	A1298C (rs1801131) C667T (rs1801133)	Altered activity Decreased activity
MTRR	A66G (rs1801394)	Altered activity
MTR	A2756G (rs1805087)	Reduced activity
SHMT	C1420T (rs1979277)	Reduced red blood cell folate levels.
RFC1	G80A (rs1051266)	Unknown
TS	Tandem repeat polymorphism in the 5-prime un-translated region	Triple-repeat allele results in higher TYMS expression
DNA repair pathway		
ERCC2	A35931C (rs13181) G23591A (rs1799793)	
XRCC1	C26304T (rs1799782) G27466A (rs25489) G28152A (rs25487)	Defective polymerase β Defective polymerase β Defective polymerase β
BRCA2	rs139052578	Reduced activity
RAD51	(G135C) rs 201838885	Altered activity

studied, and it continues to evolve. Advances in understanding of chromatin structure, histone modification, transcriptional activity, DNA methylation gene mutation, have lead to an integrated approach to the role of genetic and epigenetics in carcinogenesis. The deeper understanding of the mechanisms of lymphoblastic genetic alterations and epigenetic phenomenon, opens ways to define the prognosis of this common cancer.

References

1. Li S, Liu H, Jia Y, Deng Y, Zhang L, Lu Z, et al. A Novel SNPs Detection Method Based on Gold Magnetic Nanoparticles Array and Single Base Extension. Theranostics. 2012;2(10):967-75.
2. Faber K, Glatting KH, Mueller PJ, Risch A, Hotz-Wagenblatt A.. Genome-wide prediction of splice-modifying SNPs in human genes using a new analysis pipeline called AASsites. BMC Bioinformatics. 2011;12 Suppl 4:S2.
3. Barash CI. Ethical issues in Pharmacogenetics. Drugs. 2001. http://www.actionbioscience.org/genomic/barash.html
4. Okamoto R, Ogawa S, Nowak D, Kawamata N, Akagi T, Kato M, et al. Genomic profiling of adult acute lymphoblastic leukemia by single nucleotide polymorphism oligonucleotide microarray and comparison to pediatric acute lymphoblastic leukemia. haematologica. 2010;95(9):1481-8.
5. Pui CH, Relling MV, Downing JR. Acute lymphoblastic leukemia. New England Journal of Medicine. 2004;350(15):1535-48.
6. Stanulla M, Schrappe M, editors. Treatment of childhood acute lymphoblastic leukemia. Semin Hematol. 2009;46(1):52-63.
7. Tucci F, Aricò M. Treatment of pediatric acute lymphoblastic leukemia. haematologica. 2008;93(8):1124-8.
8. Pui CH, Evans WE. Treatment of acute lymphoblastic leukemia. New England Journal of Medicine. 2006;354(2):166-78.
9. Melega S, Canistro D, Pagnotta E, Iori R, Sapone A, Paolini M. Effect of sprout extract from Tuscan black cabbage on xenobiotic-metabolizing and antioxidant enzymes in rat liver. Mutat Res. 2013;751(1):45-51.
10. Krajinovic M, Labuda D, Sinnett D. Childhood acute lymphoblastic leukemia: genetic determinants of susceptibility and disease outcome. Reviews on environmental health. 2001;16(4):263-80.
11. Gilsing AMJ, Berndt SI, Ruder EH, Graubard BI, Ferrucci LM, Burdett L, et al. Meat-related mutagen exposure, xenobiotic metabolizing gene polymorphisms and the risk of advanced colorectal adenoma and cancer. Carcinogenesis. 2012;33(7):1332-9.
12. Yeh CC, Sung FC, Tang R, Chang-Chieh CR, Hsieh LL. Polymorphisms of cytochrome P450 1A2 and N-acetyltransferase genes, meat consumption, and risk of colorectal cancer. Diseases of the colon & rectum. 2009;52(1):104-11.
13. Silveira VS, Canalle R, Scrideli CA, Queiroz RGP, Tone LG. Role of the CYP2D6, EPHX1, MPO, and NQO1 genes in the susceptibility to acute lymphoblastic leukemia in Brazilian children. Environmental and molecular mutagenesis. 2010;51(1):48-56.
14. Zaker F, Safaei A, Nasiri N, Abdollahzadeh M, Pazhakh V. The Association of NAD(P)H:quinine Oxidoreductase Gene Polymorphisms With Pediatric Acute Lymphoblastic Leukemia. Labmedicine. 2012;43(6):256-61.
15. Ross D, Kepa JK, Winski SL, Beall HD, Anwar A, Siegel D. NAD (P) H: quinone oxidoreductase 1 (NQO1): chemoprotection, bioactivation, gene regulation and genetic polymorphisms. Chemico-biological interactions. 2000;129(1):77-97.
16. Asher G, Lotem J, Kama R, Sachs L, Shaul Y. NQO1 stabilizes p53 through a distinct pathway. Proceedings of the National Academy of Sciences. 2002;99(5):3099-104.
17. Ross D, Siegel D. NAD (P) H: quinone oxidoreductase 1 (NQO1, DT-diaphorase), functions and pharmacogenetics. Methods in enzymology. 2004;382:115-44.
18. Metodiewa D, Jaiswal AK, Cenas N, Dickancaité E, Segura-Aguilar J. Quercetin may act as a cytotoxic prooxidant after its metabolic activation to semiquinone and quinoidal product. Free Radic Biol Med. 1999;26(1-2):107-16.
19. Georgiadis P, Topinka J, Vlachodimitropoulos D, Stoikidou M, Gioka M, Stephanou G, et al. Interactions between CYP1A1 polymorphisms and exposure to environmental tobacco smoke in the modulation of lymphocyte bulky DNA adducts and chromosomal aberrations. Carcinogenesis. 2005;26(1):93-101.
20. Somner J, McLellan S, Cheung J, Mak Y, Frost ML, Knapp KM, et al. Polymorphisms in the P450 c17 (17-hydroxylase/17, 20-Lyase) and P450 c19 (aromatase) genes: association with serum sex

steroid concentrations and bone mineral density in postmenopausal women. J Clin Endocrinol Metab. 2004 Jan;89(1):344-51.
21. Lee KM, Ward MH, Han S, Ahn HS, Kang HJ, Choi HS, et al. Paternal smoking, genetic polymorphisms in CYP1A1 and childhood leukemia risk. Leuk Res. 2009 Feb;33(2):250-8.
22. Razmkhah F, Pazhakh V, Zaker F, Atashrazm F, Sheikhi M. Frequency of CYP1A1* 2C Polymorphism in Patients with Leukemia in the Iranian Population. Lab Medicine. 2011;42(4):220-3.
23. Luo W, Kinsey M, Schiffman JD, Lessnick SL. Glutathione S-transferases in pediatric cancer. Front Oncol. 2011;1:39.
24. Rossini A, Rapozo DCM, Amorim LMF, Macedo JMB, Medina R, Neto JFN, et al. Frequencies of GSTM1, GSTT1, and GSTP1 polymorphisms in a Brazilian population. Genet Mol Res. 2002;1(3):233-40.
25. Ballatori N. Transport of toxic metals by molecular mimicry. Environmental health perspectives. Environ Health Perspect. 2002;110 Suppl 5:689-94.
26. Sheehan D, Meade G, Foley VM, Dowd CA. Structure, function and evolution of glutathione transferases: implications for classification of non-mammalian members of an ancient enzyme superfamily. Biochem J. 2001;360(Pt 1):1-16.
27. Autrup H. Genetic polymorphisms in human xenobiotica metabolizing enzymes as susceptibility factors in toxic response. Mutation research. 2000;464(1):65.
28. Gundacker C, Komarnicki G, Jagiello P, Gencikova A, Dahmen N, Wittmann KJ, et al. Glutathione-S-transferase polymorphism, metallothionein expression, and mercury levels among students in Austria.. Sci Total Environ. 2007 Oct 15;385(1-3):37-47.
29. Urayama KY, Wiencke JK, Buffler PA, Chokkalingam AP, Metayer C, Wiemels JL. MDR1 gene variants, indoor insecticide exposure, and the risk of childhood acute lymphoblastic leukemia. Cancer Epidemiol Biomarkers Prev. 2007;16(6):1172-7.
30. Schinkel AH, editor. The physiological function of drug-transporting P-glycoproteins. Seminars in cancer biology; 1997: Elsevier.
31. Chaudhary PM, Roninson IB. Expression and activity of P-glycoprotein, a multidrug efflux pump, in human hematopoietic stem cells. Cell. 1991;66(1):85-94.
32. Semsei ÁF, Erdélyi DJ, Ungvári I, Kámory E, Csókay B, Andrikovics H, et al. Association of some rare haplotypes and genotype combinations in the MDR1 gene with childhood acute lymphoblastic leukaemia.Leuk Res. 2008;32(8):1214-20.
33. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nature Reviews Cancer. 2003;3(9):639-49.
34. Wiemels JL, Smith RN, Taylor GM, Eden OB, Alexander FE, Greaves MF. Methylenetetrahydrofolate reductase (MTHFR) polymorphisms and risk of molecularly defined subtypes of childhood acute leukemia. Proceedings of the National Academy of Sciences. 2001;98(7):4004-9.
35. Krajinovic M, Lamothe S, Labuda D, Lemieux-Blanchard É, Théorêt Y, Moghrabi A, et al. Role of MTHFR genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. Blood. 2004;103(1):252-7.
36. Balta G, Yuksek N, Ozyurek E, Ertem U, Hicsonmez G, Altay C, et al. Characterization of MTHFR, GSTM1, GSTT1, GSTP1, and CYP1A1 genotypes in childhood acute leukemia. American journal of hematology. 2003;73(3):154-60.
37. Zintzaras E, Koufakis T, Ziakas PD, Rodopoulou P, Giannouli S, Voulgarelis M. A meta-analysis of genotypes and haplotypes of methylenetetrahydrofolate reductase gene polymorphisms in acute lymphoblastic leukemia. European journal of epidemiology. 2006;21(7):501-10.
38. Blount BC, Mack MM, Wehr CM, MacGregor JT, Hiatt RA, Wang G, et al. Folate deficiency causes uracil misincorporation into human DNA and chromosome breakage: implications for cancer and neuronal damage. Proceedings of the National Academy of Sciences. 1997;94(7):3290-5.
39. Das PM, Singal R. DNA methylation and cancer. Journal of Clinical Oncology. 2004;22(22):4632-42.
40. Pereira TV, Rudnicki M, Pereira AC, Pombo-de-Oliveira MS, Franco RF. 5, 10-Methylenetetrahydrofolate reductase polymorphisms and acute lymphoblastic leukemia risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(10):1956-63.
41. Gemmati D, Ongaro A, Scapoli GL, Della Porta M, Tognazzo S, Serino ML, et al. Common gene polymorphisms in the metabolic folate and methylation pathway and the risk of acute lymphoblastic leukemia and non-Hodgkin's lymphoma in adults. Cancer Epidemiol Biomarkers Prev. 2004;13(5):787-94.
42. Petra BG, Janez J, Vita D. Gene-gene interactions in the folate metabolic pathway influence the risk for acute lymphoblastic leukemia in children. Leuk Lymphoma. 2007;48(4):786-92.

43. Atashrazm F, Zaker F, Aghaeipour M, Pazhakh V. Polymorphisms of the Methylene Tetrahydrofolate Reductase and Susceptibility to Acute Lymphoblastic Leukemia in Children. Lab Medicine. 2011;42(5):275-9.
44. de Jonge R, Tissing WJE, Hooijberg JH, Jansen G, Kaspers GJL, Lindemans J, et al. Polymorphisms in folate-related genes and risk of pediatric acute lymphoblastic leukemia. Blood. 2009;113(10):2284-9.
45. Belkov VM, Krynetski EY, Schuetz JD, Yanishevski Y, Masson E, Mathew S, et al. Reduced folate carrier expression in acute lymphoblastic leukemia: a mechanism for ploidy but not lineage differences in methotrexate accumulation. Blood. 1999;93(5):1643-50.
46. de Deus DMV, de Lima ELS, Seabra Silva RM, Leite EP, Cartaxo Muniz MT. Influence of Methylenetetrahydrofolate Reductase C677T, A1298C, and G80A Polymorphisms on the Survival of Pediatric Patients with Acute Lymphoblastic Leukemia. Leuk Res Treatment. 2012;2012:292043. Epub 2012 Oct 17.
47. Schnakenberg E, Mehles A, Cario G, Rehe K, Seidemann K, Schlegelberger B, et al. Polymorphisms of methylenetetrahydrofolate reductase (MTHFR) and susceptibility to pediatric acute lymphoblastic leukemia in a German study population. BMC medical genetics. 2005;6(1):23.
48. Yu K, Zhang J, Dou C, Gu S, Xie Y, Mao Y, et al. Methionine synthase A2756G polymorphism and cancer risk: a meta-analysis. European Journal of Human Genetics. 2009;18(3):370-8.
49. Goode EL, Potter JD, Bigler J, Ulrich CM. Methionine synthase D919G polymorphism, folate metabolism, and colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev. 2004 Jan;13(1):157-62.
50. Heil SG, Van der Put NMJ, Waas ET, den Heijer M, Trijbels FJM, Blom HJ. Is mutated serine hydroxymethyltransferase (SHMT) involved in the etiology of neural tube defects? Molecular genetics and metabolism. 2001;73(2):164-72.
51. Gangjee A, Jain HD, Phan J, Lin X, Song X, McGuire JJ, et al. Dual Inhibitors of Thymidylate Synthase and Dihydrofolate Reductase as Antitumor Agents: Design, Synthesis, and Biological Evaluation of Classical and Nonclassical Pyrrolo [2, 3-d] pyrimidine Antifolates 1. Journal of medicinal chemistry. 2006;49(3):1055-65.
52. Lightfoot TJ, Johnston WT, Painter D, Simpson J, Roman E, Skibola CF, et al. Genetic variation in the folate metabolic pathway and risk of childhood leukemia. Blood. 2010;115(19):3923-9.
53. Stanczyk M, Sliwinski T, Cuchra M, Zubowska M, Bielecka-Kowalska A, Kowalski M, et al. The association of polymorphisms in DNA base excision repair genes XRCC1, OGG1 and MUTYH with the risk of childhood acute lymphoblastic leukemia. Molecular biology reports. 2011;38(1):445-51.
54. Friedenson B. The BRCA1/2 pathway prevents hematologic cancers in addition to breast and ovarian cancers. BMC Cancer. 2007 Aug 6;7:152.
55. Chokkalingam AP, Bartley K, Wiemels JL, Metayer C, Barcellos LF, Hansen HM, et al. Haplotypes of DNA repair and cell cycle control genes, X-ray exposure, and risk of childhood acute lymphoblastic leukemia. Cancer Causes Control. 2011;22(12):1721-30.
56. Vijayakrishnan J, Houlston RS. Candidate gene association studies and risk of childhood acute lymphoblastic leukemia: a systematic review and meta-analysis. haematologica. 2010;95(8):1405-14.
57. Zhang Z, Yang L, Zhang Y, Yang Y, Nie L, Li L, et al. Relationship between NQO1C (609T), RAD51 (G135C), XRCC3 (C241T) single nucleotide polymorphisms and acute lymphoblastic leukemia]. Zhongguo Shi Yan Xue Ye Xue Za Zhi. 2009;17(3):523-8. (Abstract).
58. Whitehouse CJ, Taylor RM, Thistlethwaite A, Zhang H, Karimi-Busheri F, Lasko DD, et al. XRCC1 stimulates human polynucleotide kinase activity at damaged DNA termini and accelerates DNA single-strand break repair. Cell. 2001;104(1):107-17.
59. Joseph T, Kusumakumary P, Chacko P, Abraham A, Pillai MR. DNA repair gene XRCC1 polymorphisms in childhood acute lymphoblastic leukemia. Cancer lett. 2005;217(1):17-24.
60. Pakakasama S, Sirirat T, Kanchanachumpol S, Udomsubpayakul U, Mahasirimongkol S, Kitpoka P, et al. Genetic polymorphisms and haplotypes of DNA repair genes in childhood acute lymphoblastic leukemia. Cancer Causes Control. 2011;22(9):1243-58.
61. Batar B, Güven M, Barış S, Celkan T, Yıldız İ. DNA repair gene XPD and XRCC1 polymorphisms and the risk of childhood acute lymphoblastic leukemia. Leukemia research. 2009;33(6):759-63.
62. Meza-Espinoza J, Peralta-Leal V, Gutierrez-Angulo M, Macias-Gomez N, Ayala-Madrigal M, Barros-Nuñez P, et al. XRCC1 polymorphisms and haplotypes in Mexican patients with acute lymphoblastic leukemia. Genet Mol Res. 2009;8:1451-8.
63. Tumer TB, Yilmaz D, Tanrikut C, Sahin G, Ulusoy G, Arinç E. DNA repair XRCC1 Arg399Gln polymorphism

alone, and in combination with CYP2E1 polymorphisms significantly contribute to the risk of development of childhood acute lymphoblastic leukemia. Leukemia research. 2010;34(10):1275-81.
64. Canalle R, Silveira VS, Alberto Scrideli C, Queiroz RGP, Fernando Lopes L, Gonzaga Tone L. Impact of thymidylate synthase promoter and DNA repair gene polymorphisms on susceptibility to childhood acute lymphoblastic leukemia. Leuk Lymphoma. 2011 Jun;52(6):1118-26.
65. Karathanasis NV, Choumerianou DM, Kalmanti M. Gene polymorphisms in childhood ALL. Pediatr Blood Cancer. 2009 Mar;52(3):318-23.
66. Moynahan ME, Pierce AJ, Jasin M. BRCA2 is required for homology-directed repair of chromosomal breaks. Mol Cell. 2001;7(2):263-72.
67. Hoeijmakers JHJ. Genome maintenance mechanisms for preventing cancer. Mech Ageing Dev. 2007;128(7-8):460-2.
68. Moorman AV, Harrison CJ, Buck GAN, Richards SM, Secker-Walker LM, Martineau M, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. Blood. 2007;109(8):3189-97.
69. Zakaria Z, Ahid M, Fadly M, Ismail A, Ten SK, Mohamad Nor N, et al. Chromosomal Aberrations in ETV6/RUNX1-positive Childhood Acute Lymphoblastic Leukemia using 244 K Oligonucleotide Array Comparative Genomic Hybridization. Mol Cytogenet. 2012;5(1):41.
70. Pear WS, Aster JC. T cell acute lymphoblastic leukemia/lymphoma: a human cancer commonly associated with aberrant NOTCH1 signaling. Current opinion in hematology. 2004;11(6):426-33.
71. Messinger YH, Higgins RR, Devidas M, Hunger SP, Carroll AJ, Heerema NA. Pediatric acute lymphoblastic leukemia with at (8; 14)(q11. 2; q32): B-cell disease with a high proportion of Down syndrome: a Children's Oncology Group study. Cancer Genetics. 2012;205(9):453-8.
72. Harrison CJ. Acute lymphoblastic leukaemia. Best Practice & Research Clinical Haematology. 2001;14(3):593-607.
73. Harrison CJ. The detection and significance of chromosomal abnormalities in childhood acute lymphoblastic leukaemia. Blood reviews. 2001;15(1):49-59.
74. Chessells JM. Acute lymphoblastic leukaemia.2001, eLS. http://onlinelibrary.wiley.com/doi/10.1038/npg.els.0002172/full
75. Popovic R, Licht JD. Emerging epigenetic targets and therapies in cancer medicine. Cancer Discovery. 2012;2(5):405-13.
76. Nakazawa T, Kondo T, Ma D, Niu D, Mochizuki K, Kawasaki T, et al. Global histone modification of histone H3 in colorectal cancer and its precursor lesions. Human pathology. 2012;43(6):834-42.
77. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010;31(1):27-36.
78. Garcia-Manero G, Daniel J, Smith TL, Kornblau SM, Lee MS, Kantarjian HM, et al. DNA methylation of multiple promoter-associated CpG islands in adult acute lymphocytic leukemia. Clin Cancer Res. 2002 Jul;8(7):2217-24.
79. Kuang S, Tong W, Yang H, Lin W, Lee M, Fang Z, et al. Genome-wide identification of aberrantly methylated promoter associated CpG islands in acute lymphocytic leukemia. Leukemia. 2008;22(8):1529-38.
80. Kuang SQ, Bai H, Fang ZH, Lopez G, Yang H, Tong W, et al. Aberrant DNA methylation and epigenetic inactivation of Eph receptor tyrosine kinases and ephrin ligands in acute lymphoblastic leukemia. Blood. 2010;115(12):2412-9.
81. Einav Nili GY, Saito Y, Egger G, Jones PA. Cancer epigenetics: modifications, screening, and therapy. Annu Rev Med. 2008;59:267-80.
82. Garcia-Manero G, Yang H, Kuang SQ, O'Brien S, Thomas D, Kantarjian H, editors. Epigenetics of acute lymphocytic leukemia. Seminars in hematology; 2009: Elsevier.
83. Agirre X, Roman-Gomez J, Jimenez-Velasco A, Garate L, Montiel-Duarte C, Navarro G, et al. ASPP1, a common activator of TP53, is inactivated by aberrant methylation of its promoter in acute lymphoblastic leukemia. Oncogene. 2005;25(13):1862-70.
84. Garcia-Manero G, Bueso-Ramos C, Daniel J, Williamson J, Kantarjian HM, Issa JPJ. DNA methylation patterns at relapse in adult acute lymphocytic leukemia. Clinical Cancer Research. 2002;8(6):1897-903.
85. Dunwell TL, Hesson LB, Pavlova TV, Zabarovska V, Kashuba VI, Catchpoole D, et al. Epigenetic analysis of childhood acute lymphoblastic leukemia. Epigenetics. 2009;4(3):185-93.
86. Zhang L, Freitas MA, Wickham J, Parthun MR, Klisovic MI, Marcucci G, et al. Differential expression

of histone post-translational modifications in acute myeloid and chronic lymphocytic leukemia determined by high-pressure liquid chromatography and mass spectrometry. Journal of the American Society for Mass Spectrometry. 2004;15(1):77-86.

87. Li X, Liu J, Zhou R, Huang S, Chen XM. Gene silencing of MIR22 in acute lymphoblastic leukaemia involves histone modifications independent of promoter DNA methylation. British journal of haematology. 2010;148(1):69-79.