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Risk factors of pediatric acute lymphoblastic leukemia: A review

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Abstract
Background: Pediatric cancers are one of the most common diseases growing worldwide and are categorized into acute lymphocytic leukemia, acute myelogenous leukemia, chronic lymphocytic leukemia, and chronic myelogenous leukemia, and the most common form of childhood leukemia is ALL.
Aim: In this review, we tried to grasp different risk elements of ALL and the complexity of ALL.
Method: Concerning the data collection, different keywords were used for the data retrieval from the different online repositories were utilized which include PubMed, Medline, Web of Science, etc.
Result: It was plethora of risk factors was found to increases the risk of ALL in pediatrics which includes paternal alcoholic consumption, smoking habits, and maternal & paternal age, are important contributors to the risk of ALL in the child. Different changes at chromosomal level and also at gene level were found to be an important contributor for determining the susceptibility of ALL in pediatrics. Also, different inherited syndromes were found comorbid with the risk of ALL in children, with predisposing recessive mutation inherited from parents to offspring.
Discussion & Conclusion: It is concluded that ALL is a very complex disorder where genetic alteration is the prime factor for determining the risk of diseases and concerning the ALL in pediatrics, maternal and paternal life style factors are import for lowering the threshold of susceptibility of diseases. Therefore, it is important to prevent or limit the exposure to various environmental risk attributes and thus help in lowering the diseases susceptibility.

Keywords: ALL, risk factors, environmental factors, genetic and molecular factors

Introduction
Biomass is the main source of fuel both in the rural and urban areas within countries like Pediatric cancers are one of the deadliest diseases growing worldwide which range between 0-15 years of age (Arora and Arora 2016) [1]. It has been estimated that alone in India, annually around 45,000 children are diagnosed with cancer which is the ninth most common factor leading to death in children between 5-14 years (Asthana *et al*., 2018) [2]. One such astonishing example of childhood cancer is the blood cancer commonly known as Leukemia. Regarding sucha "sea of lymphoblastic", leukemia is characterized by malignant proliferation and accumulation of abnormal hematopoietic cells in the bone marrow (Shukla *et al*., 2020) [3]. Categorization of leukemia based on criteria "which type of cell (myeloid or lymphoid) &progression period i.e., acute develop quickly and chronic develop slowly", different range of types has been characterized such as Acute Lymphocytic Leukemia (ALL), Acute Myelogenous Leukemia (AML), Chronic Lymphocytic Leukemia (CLL), and Chronic Myelogenous Leukemia (CML). The most common form of childhood leukemia is "ALL" can develop from any lymphoid cell (T-cell or B-cell) blocked at a particular stage of development including primitive cells with multiline age potential (Campos-Sanchez *et al*., 2011; Shukla *et al*., 2020) [88, 3]. The incidence of "ALL" is highest in children below 15 years of age and the peak is seen in the age group of 2-7 years (Greenlee *et al*., 2000) [66] with preponderance among boys (Belson *et al*., 2007**)** [89]. Regarding the newly diagnosed cases, it has been found that about 2200 cases of childhood leukemia are diagnosed annually in the US, where around 79% of cases are ALL, followed by AML.

Concerning the vital statistical estimates of pediatric acute lymphoblastic leukemia, the global burden of Disorder-2019 has shown that China has the highest prevalent cases with 79,840.14 / 100,000 per year followed by India (10,647.06 / 100,000). For India, the highest prevalence has been recorded in the state of Uttar Pradesh with 2,129.77, followed by Bihar and Maharashtra with 1,078.31 and 1,005.11 respectively (Figure 1A) (GBD India Compare | IHME *Viz* Hub (healthdata.org).According to the reports of NCRP 2020, the cancer load varies across the length and breadth of the country with the maximum cases in the northern region of India and least in the North-Eastern region (Ncdirindia.org) (Figure 1A). During the last few years, in India alone, ALL is responsible for a significant death (Figure 1B), where the maximum death was found in the pediatric groups (<18 years) (Causes of Death (COD) Visualization | IHME *Viz* Hub (healthdata.org) and poor survival rate might be the reason (Arora and Arora, 2016) [1].

ALL is the most common type in children worldwide and spreads very fast in the body and thus requires urgent treatment. The disease is featured with some warning signs and symptoms before they harbor the body and start interrupting the normal development of hematopoietic cells. These include bone and joint pain, feeling tired and weak, decrease in the RBCs count, loss in platelets, feeling dizzy or lightheaded, shortness of breath, prolonged fever, bruises and bleeding, severe night sweats, loss of appetite, swollen lymph nodes, sometimes chest pain, vomit, breathing problem, pale skin (Figure 2A) (Terwilliger & Abdul-Hay, 2017) [4]. Several risk factors like certain environmental factors including radiations, chemicals, pesticides, smoking, tobacco, alcohol, inherited syndromes, genetic /molecular variables, etc.,(Figure 2B) is involved in the differentiation and the proliferation of lymphoid precursor cells. Therefore, the goal of authoring this mini-review version was to compile various data about risk attributes into a single document that might serve as a summary of the risk factors associated with pediatric acute lymphoblastic leukemia.

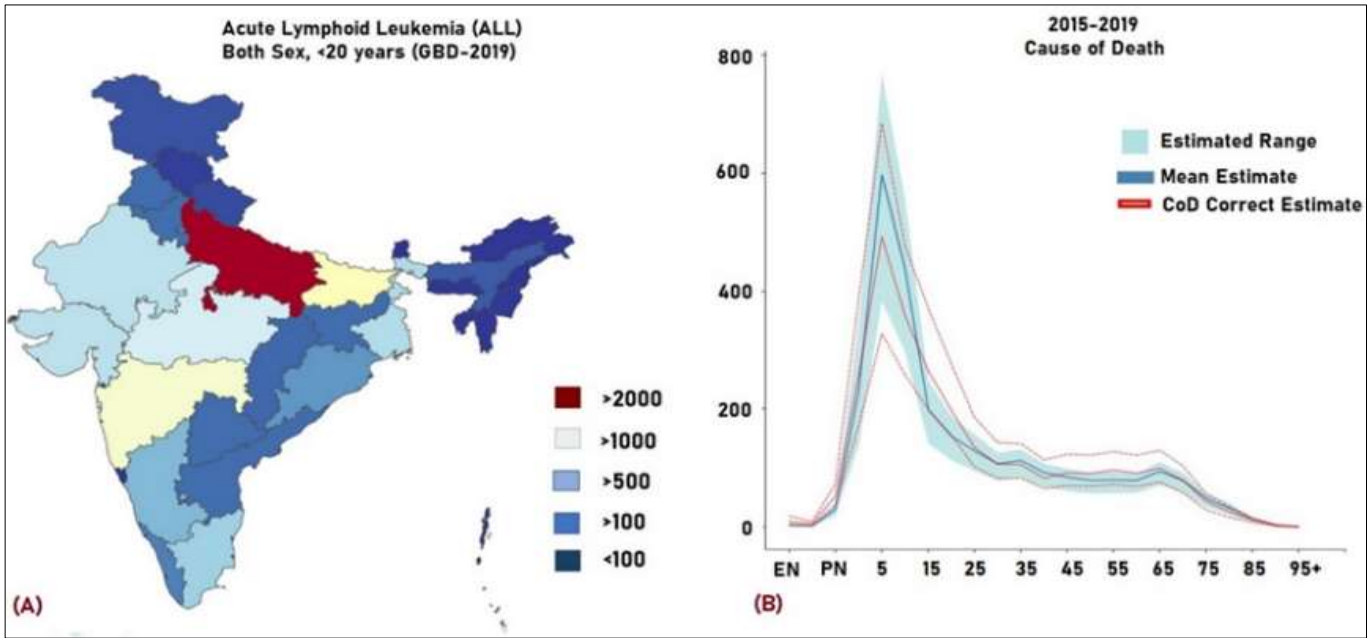

Fig 1A: The highest prevalence has been recorded in the state of Uttar Pradesh with 2,129.77, followed by Bihar and Maharashtra with 1,078.31 and 1,005.11 respectively (GBD India Compare | IHME *viz* Hub (healthdata.org).
(B): In India, ALL is responsible for a significant death where the maximum death was found in the pediatric groups (<18 years) (Causes of Death (COD) Visualization | IHME *viz* Hub (healthdata.org).

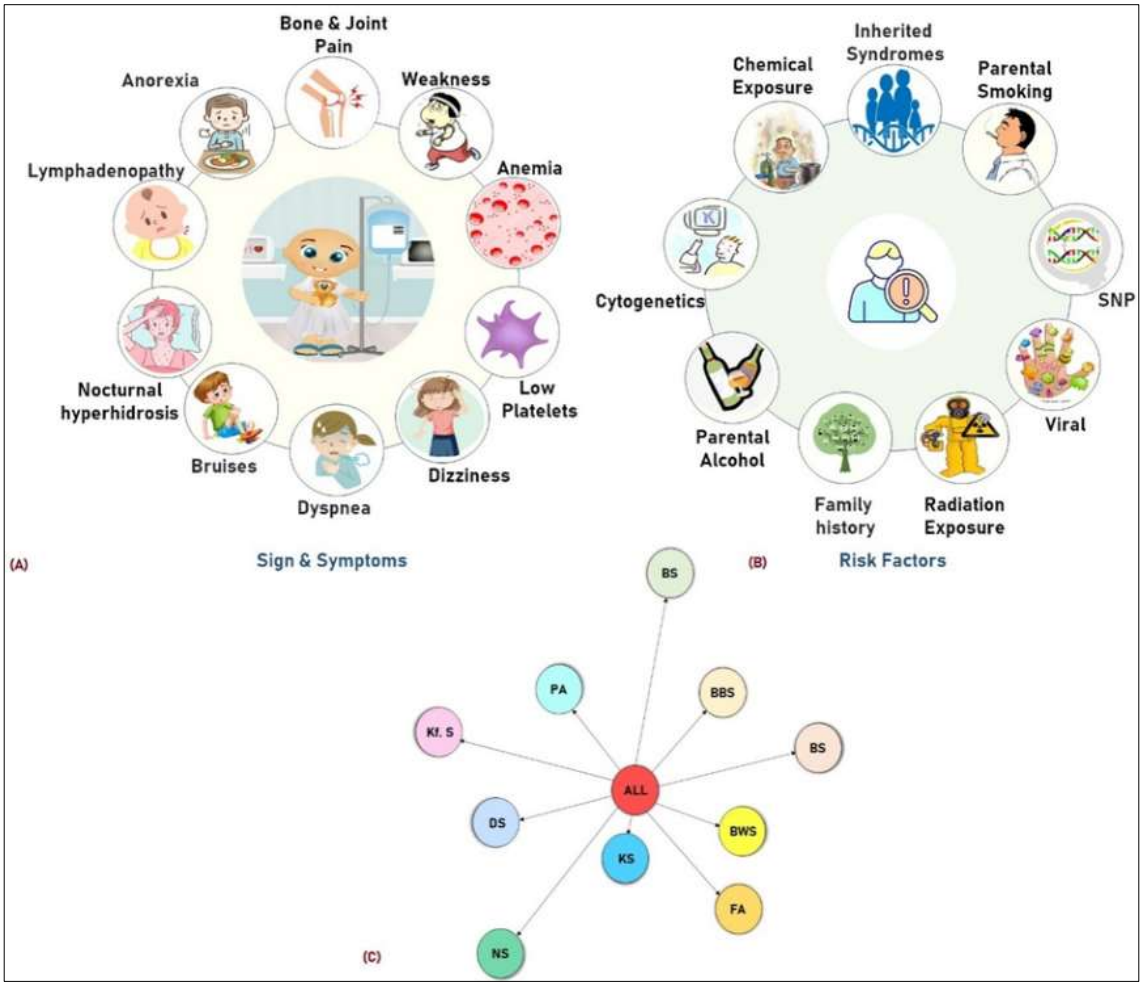

Fig 2: A: Sign and symptoms associated with AML. (B): Diverse range of risk variables responsible for increasing the risk susceptibility of AML.(C): Comorbidity network ALL: Acute Lymphoblastic Leukemia, BBS: Bardet–Biedl syndrome, BWS: Beckwith-Wiedemann syndrome, BS: Bloom syndrome, FA: Fanconi Anemia, Kf. S: Klinefelter syndrome, AT: Ataxia telangiectasia, DS: Down Syndrome, NS: Netherton syndrome

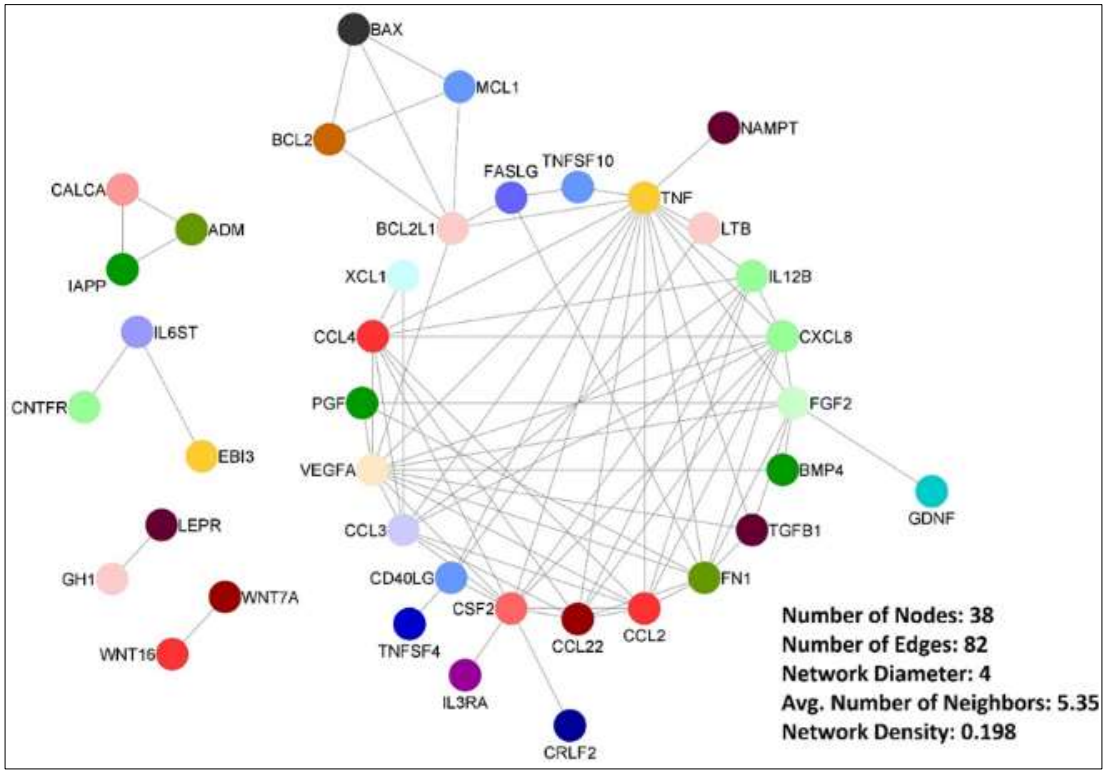

Fig 3: Network of genes responsible from the increase risk of ALL (Download: DisGeNET -Database of gene-disease associations) Network created by Cytoscape: Cytoscape: An Open Source Platform for Complex Network Analysis and Visualization).

Methodology

Concerning the data collection, data retrieving strategies from the different online repositories were utilized which include PubMed (PubMed (nih.gov), Medline (Medline.com | Medline Industries, Inc), Web of Science (Clarivate), etc. A mixture of keywords was used for data retrievals, such as analyses regarding the incidence rates of leukemia, genetic changes in ALL, chromosomal abnormalities as risk factors for acute lymphoblastic Leukemia, genetic polymorphism, etc. Our main concern was the risk factors associated with the increased risk of childhood ALL. Therefore, all authors checked the downloaded literature carefully.

Background

Risk factors

Risk factors are defined as the factors responsible for increasing the risk susceptibility of disease. Different factors have been discovered in the last decades (Figure 3B) and are discussed below.

Paternal or maternal smoking / tobacco / alcohol consumption

Smoking is one of the well-established risk factors for leukemia whether it is an adult cigarette smoker (Fircanis *et al*., 2014) [5] or an infant (Liu *et al*., 2011) [6]. Smoking during pregnancy or pre-pregnancy for the parents is a well-established factor for an infant's increased risk of developing ALL (Shu *et al*., 1996; Ferreira *et al*., 2012; Cao *et al*., 2020) [7, 93, 94]. Paternal smoking directly affects the quality of sperm by oxidative damage and causing sperm aneuploidy (Fraga *et al*., 1996, Shi *et al*., 2001, Chang *et al*., 2006) [9, 10, 100] and is possibly inherited with such detrimental changes.

It is important to think about stopping smoking because the risk of diseases was higher in those infants whose mothers were smoking 3 months before conception as compared to those who left smoking during the same period (Chang *et al*., 2005) [8]. Similarly, paternal smoking also showed the same results in the case of heavy smokers for a lifetime (p<0.05), and the overall risk increased was 1.2-1.3-fold (Milne *et al*., 2013) [11]. Smoking is responsible for the addition of chromosomal abnormalities at higher rates. Joint exposure to paternal smoking during in-utero or after parturition, the effect of smoking has been seen to increase the risk of developing childhood ALL (Pluth *et al*., 2000; John *et al*., 1991) [12-13].

Metayer and group gave some astonishing results that pointed toward the ethnic association and the effect of smoking and ALL (Metayer *et al*., 2016) [14]. They found an increased risk of ALL in the Hispanic population with maternal smoking (OR =2.08, 95% confidence interval (CI): 1.20, 3.61) but this association was absent in ethnic groups. In contrast, several studies in UK and USA maternal smoking during the gestation period showed no significant association with infant ALL (Brondum *et al*., 1999, Pang *et al*., 2003) [67, 15].

Alcohol is considered a potent carcinogenic compound and it has been suggested that maternal alcohol consumption in the increased risk of childhood Leukemia (Shu *et al*. 1996; Latino-Martel *et al*. 2010; Skibola *et al*. 2014; Infante and El-Zein, 2007; Latino-Martel *et al*., 2010) [7, 77, 17, 68, 77] in contrast negative association studies (Milne *et al*., 2013) [11].

Other than smoking and alcohol consumption, different parental factors such as maternal and paternal education level, birth order and parental occupational exposure, and paternal age at child's birth, are some risk attributes that linearly correlate with the risk of pediatric AML (Panagopoulou *et al*., 2019) [78].

Radiation exposure

It is a well-known fact that ionization rays are one of the key causative agents of leukemia as it is very carcinogenic (Leuraud *et al*., 2015) [79]. Exposure to high ion radiations is well established during childhood or the fetal developmental period (Boice *et al*., 1999) [18] but the question is, does the low ionization rays could be a reason for an increased risk of leukemia? Wake ford and group after studying the post effects of Japanese bomb survivors and childhood cancers found that low ionization / low-frequency radiations/ low dose or low dose-rate exposure has shown significant effective relative risk on childhood leukemia cases in the Japanese population (Wakeford *et al*., 2013) [19]. Exposure to ionizing radiation at cumulative doses <100 mSV is sufficient to increase the risk to develop acute myeloid leukemia and ALL by changing the gene sequences (Berrington *et al*. 2016) [20].

Moysich and group studied the Chornobyl-related ionizing radiation exposure and cancer risk in children and found no conclusive results for leukemia but pointed out that the number of infants with leukemia was in large number in the European region after the incidence (Moysich *et al*. 2002) [21]. Ha and group after studying Radio-frequency radiation exposure from AM radio transmitters and childhood leukemia and brain cancers suggested a possible carcinogenic effect of Amplitude modulation Radio-frequency radiation (AM RFR exposure on children, particularly concerning lymphocytic leukemia (Ha *et al*. 2007) [22] and a strong exposure effect have been seen for those who lived near the AM RFR areas within 2 kilometers. But the incidence of infant leukemia showed no such connection when distance was taken as the factor (Rashed *et al*., 2019) [69].

To this end, it does not matter whether you are exposed to low or high ionization radiation, or static magnetic fieldsthe chance of risk of diseases is equal and thus more concern should be taken (Calvente *et al*. 2010) [23].

Chemical exposure

Several studies have shown the effect of chemical exposure in different forms and different stages and leading to an increased risk of childhood leukemia. Exposure of mothers to certain gene-modifying chemicals like topo-II inhibitor drugs and mosquito repellents like bayonets have been found to increase the risk of infant acute Leukemia (Alexander *et al*. 2001; Pelkonen *et al*,.2017) [24-25]. Parent occupation and risk of acute leukemia have also been correlated (Zhang *et al*., 2009) [26] in children especially those dealing with Formaldehyde exposure, (Ferreira *et al*., 2013) [27] pesticide exposure, (Hernández & Menéndez, 2016) [92] environmental radon exposure (Tong *et al*., 2012), benzene which is used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, present in cigarette, glues, cleaning products, detergents paint, etc. are import risk attributes (Belson *et al*., 2007) [89].

Viral Infection

It is important to understand that, viruses have capabilities that their genetic material once inserted into the genome of

the host can cause a serious problem and one such example is cancer (Moore & Chang, 2010) [28]. Certain viral infections like HTLV-1, Epstein-bar-virus, etc. are said to be associated with different leukemia but going through the literature the outcomes showed that ALL patients are prone to several viral infections as their immunity is decreased and it further deteriorates when undergoing chemotherapies. Koskenvua and group found the rate of infections to be 44% with a maximum percent of human Boca virus (5%), and influenza A virus (4%). rhinovirus (22%), respiratory syncytial virus (11%), and pneumonia with cough, and (Koskenvua *et al*., 2008) [29]. It has been well known established that, 16 herpes simplex, 7 varicella, 10 herpes zoster infections (varicella-zoster virus (VZV), and several gram-negative and gram-positive bacteria cause infection in ALL patients (Wood and Corbitt 1985) [30]. Couch and Englund observed that several viruses cause problems in "ALL-children" and those include influenza viruses, respiratory syncytial virus, para influenza viruses, (RSV), rhinoviruses, coronaviruses, and adenoviruses (Couch and Englund, 1997) [31].

Family history of leukemia

Several studies have depicted a correlation between a family history of cancer and the risk of leukemia as it may be due to the shared genetic risk factors for the disease (Rauscher *et al*., 2002) [32]. Several studies have shown a strong relationship between the rate of consanguinity and family history and leukemia incidences (Bener *et al*., 2001; Kakaje *et al*., 2020) [71, 95]. Studied the family history of cancer and its role and association with the etiology of childhood hematopoietic malignancies, Rudant, and colleagues carried out a population-based case-control study, in the French population. They observed that association with family history when two members of the family were infected revealed these results with an increased risk of non-Hodgkin and Hodgkin lymphoma but fewer associations were found with Acute Leukemia (Rudant *et al*., 2007) [72].

Considering the family history of different diseases, it has been observed that there is an increased risk between childhood cancers and family history of diseases including leukemia and brain tumors (Kuijten *et al*., 1993) [33] Alteiri and group enlightened the various factors like sibling number or the birth order of the child also plays a role in the onset of certain genes that can lead to leukemia/lymphoma and found that the older siblings have a protective effect as compared to the younger ones (Alteiri *et al*., 2006) [92]. Concerning the survival rate of cancer patients, Anderson and colleagues pointed out that the survival rate is not affected by the family history of cancers or their rate of survival (Anderson *et al*., 2007) [99]. Family history and the association between lymphomas and other childhood cancers have also been shown having related by other studies and high risk with first-degree relatives (Chang *et al*., 2005; Cuttner *et al*., 1992; Chiu *et al*., 2004) [8, 35, 36].

Inherited syndromes

Comorbidity is a well-known concept, which is defined as the co-occurrence of two disorders, and concerning pediatric acute lymphoblastic Leukemia, diverse inherited syndromes were found to be comorbid such as Beckwith–Wiedemann syndrome (BWS), cleidocranial dysostosis (Wilmstumor), Bardet-Biedl syndrome (BBS) (acute lymphoblastic leukemia), Kabuki syndrome (neuroblastoma), LEOPARD syndrome (neuroblastoma), Poland anomaly (osteosarcoma; Hodgkin disease), and blepharophimosis epicanthus inversus syndrome (Burkitt lymphoma), Down syndrome (21 trisomy) (Laurent *et al*. 2020; Lejeune *et al*. 1959) [37-38], Klinefelter syndrome, (47, XXY), Fanconi anaemia, Bloom syndrome, Ataxia telangiectasia (Dutzmann *et al*., 2022) [39], neurofibromatosis, etc. (Merks *et al*., 2005; Brown *et al*., 2019) [80, 40]. A rare genetic disorder Netherton syndrome (NS) in a 15-year-old male patient with anemia, thrombocytopenia, leukocytosis, high CRP level was reported suspecting ALL (Skoczen *et al*. 2020) [41]. Some syndromes affected people like Noonan syndrome (NS), constitutional mismatch repair deficiency (CMMRD), Neurofibromatosis 1 (NF1), and Li-Fraumeni syndrome (LFS).Such comorbidities can be defined by the predisposition of certain genes which are shared by those genetic disorders and thus are responsible for many neoplasia cases in children (Kratz *et al*., 2021, Fujita *et al*., 2021) [42-43]. Recent germline studies have discovered certain aspects of association with certain genetic syndromes in the light of single nucleotide polymorphism (SNP) genotype, and genome-wide gene expression, DNA copy number (Bloom *et al*. 2019, Tebbi, 2021) [101, 45].

Cytogenetic& molecular basis of ALL

Approximately 80% of leukemia is contributed by a cytogenetic abnormality, which includes different translocations such as t between the 8th and 14th chromosome [t(8;14)] which possesses MYC-IgH (Moorman *et al*.2012), t(4;11) (MLL-AF4) in 60% of infants younger than 12 months (Pui *et al*., 2008) [47], t(9;22) (BCR-ABL1) with Philadelphia (Ph) chromosome in 2% to 5% of children and 30% of adults (Soverini *et al*. 2007; Pui *et al*. 2017) [48-49], t(1;19) TCF3-PBX1 in 30% of pre-B cell childhood ALL patients, t(12;21) ETV6-RUNX1about 25% of children and 3% of adults with B-ALL (Mellentin *et al*., 1989) [50]. Aneuploidy and translocations for the B-acute lymphoblastic leukemia (B-ALL) along with the interstitial deletion region 1 of chromosomes X and Y in B-progenitor ALL that juxtaposes the first, non-coding exon of P2RY8 with the coding region of CRLF with 7% P2RY8-CRLF2 fusion in 7% of individuals with B- ALL (Mullighan *et al*. 2009) [51]. Dicentric chromosome abnormality due to fusion of centromeres of chromosomes 9 and 20(9;20), resulting in loss of 9p and 20q material, which is a rare aberration in B-cell precursor acute lymphoblastic leukemia (Rieder *et al*. 1995, Clark *et al*., 2000, Lejman *et al*., 2022) [52-54]. Also, deletions at 9p21in the CDKN2A that includes p16/INK4A and p14/ARF suppressor genes, are seen in 70% of the T-ALL cases (Ferrando *et al*. 2002, Pui *et al*. 2008) [65, 47]. Cytogenetic analysis was found absent for BCR / ABL1, ETV6, and RUNX1 genes and MLL gene. Ph-like ALL was associated with event-free and overall survival rates equal or inferior to high-risk ALL subtypes (Roberts *et al*. 2014, Skoczen *et al*. 2020) [56, 41]. A result of treatment outcome in B-ALL Ph + patients, the chemotherapy tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib showed comparative results with the bone marrow transplant (Schultz *et al*., 2014; Chalandon *et al*., 2015) [57-58].

Recent advancements in molecular genetic technology have uncovered a lot of genes possess mutation few including SPINK5, NUP214, JAK2, IL17RC, TTN, ACTN2, TRPV3, and COL7A1 with germline mutations including p. Cys510*, p.Arg815Gln, p.Arg683Gly, p.Ala303Thr,

p.Gly1091Arg, p.Pro17245Leu, p.Ile143Leu, p.Arg729* and p.Glu2842fs respectively (Bloom *et al*. 2020, Kratz *et al*., 2021) [44, 42]. Also, the mutation in several genes mentioned by Zhang and group that are associated with ALL occurrences are somatic mutations in ALL blasts (PAX5, IKZF1, ETV6, PTPN11) (Zhang *et al*., 2012) [91]. Certain genes like RUNX1, CEBPA, GATA2, and TP53, have been used for streamlining and detecting the pediatric AML but not in the case of adult ALL (Tawana *et al*., 2018) [60]. Cancers diagnosed in the pediatric age range occur are mostly because of genetic mutations ranging between 5-10% (Kratz *et al*., 2021) [42]. Several targeted family-based studies have helped to understand different mechanisms involved in the majority of sporadic cancers and improve clinical diagnosis using whole genome sequencing, imaging about these cancer types and their treatment strategies have proved these days (Kratz *et al*., 2021) [42].

Numerous candidate gene association studies (Treviño *et al*., 2009; Furuhata *et al*., 2009, Al-Khreisat *et al*., 2022; Al-absi *et al*., 2017; Mosaad *et al*., 2019; Mahjoub *et al*., 2019; Krajinovic *et al*., 2002) [61, 62, 75, 74, 81] (Table 1) have been performed for the respective condition where it has been shown that susceptibility largely depends on the candidate genes. Apart from such associated risk attributes from case-controls designed research, their value turned out and none could be replicated in a large genome-wide marker dataset (Table 2) (GWAS Catalog (ebi.ac.uk). Such inconsistency between candidate gene studies and GWAS for leukemia might be due to diverse reasons such as low penetrance allele selection. Genetic variations with small effect sizes, as well as environmental factors (Sudershan *et al*., 2022) [64]. Such alteration of genes is responsible for the disrupted proteins which cause altered homeostasis. Activation of signaling and genetic changes in transcription factors, activating oncogenes, and tumor suppressors in developing T cell-ALL (Van& Ferrando, 2012) [65].

The gene-diseases association database (DisGeNET - Database of gene-disease associations) was utilized to enlighten the different list of signaling proteins that are mostly found to be disrupted in pediatric ALL. Complex protein-protein interaction of such signaling proteins was established by “STRING” a functional protein association network (String-db.org) and the network of complex protein-protein interaction features was analyzed by Cytoscape: an Open-Source Platform for Complex Network Analysis and Visualization (Figure 3). Such alteration of genes is responsible for the disrupted proteins which cause altered homeostasis.

Future Perspective

Cancer is characterized by the presence of six hallmarks which includes sustaining proliferative signaling, evading growth suppressors, enabling replicative immortality, resisting cell death, inducing angiogenesis, and activating invasion and metastasis (Hanahan & Weinberg, 2011) [98]. Different genes including from the families of the cell cycle, regulators of apoptosis, DNA repair, metabolism of a carcinogenic compound, regulators of extracellular matrix, etc., are important for such dys regulation of such critical pathways. Dysregulation of such genes is due to different reasons which include single nucleotide change, deletion of single/ many nucleotides, translocation, etc., which can be categorized under mutation. Another important notion, which is different from the mutation is the "heritable change in the genome that cannot be explained by mutation" which is called epigenetics (Sharma *et al*., 2010) [97] which includes histone methylation, acetylation, CpG island methylation, RNA interference, etc. Also, other than the genetic point of view which is important for determining the susceptibility of cancer, non-genetic factors or simply environmental/ lifestyle factors are important risk variables that hinder the threshold susceptibility risk and increase the risk by several folds. Here in this review, we have observed different environmental factors such as, increased exposure to ionizing radiations at cumulative doses <100 mSV is sufficient to increase the risk to develop acute myeloid leukemia and ALL by changing the gene sequences, paternal and maternal life style attributes such as exposure of mothers to certain gene-modifying chemicals like topo-II inhibitor drugs, mosquito repellents, parent occupation exposure with Formaldehyde exposure, (Ferreira *et al*., 2013) [27] pesticide exposure, (Hernández & Menéndez, 2016) [90] environmental radon exposure (Tong *et al*., 2012) [91], benzene which is used in the rubber industry, oil refineries, chemical plants, shoe manufacturing, present in cigarette, glues, cleaning products, detergents paint, etc. are import risk attributes (Belson *et al*., 2007) [89]. Also, viral infection, family history of syndrome which is directly correlated to the change/ alteration in the chromosome which is termed as chromosomal instability.

Enclosing the section, what we have learned after reviewing the is that it is impossible to change the gene or chromosomal instability, but what we can do is to limit the exposure to various life threating risk which can decreases the risk of diseases. Maternal exposure to unwanted radiation, chemicals, and pesticides should strictly be prohibited and also post-natal exposure to the child should also avoid. This basic awareness regarding these exposure levels can decrease the rate of ALL incidences in children thus expecting a healthy life for the future generation.

Table 1: Candidate genes associated with pediatric acute lymphoblastic leukemia uncovered using case-control observational study

Gene	Function	rs ID / Loci	Case/ Control	Population / Ethnicity	OR	p-Value	Reference
GSTP1	Metabolism of carcinogens	Val105 substitution	278/ 303	French-Canadian	1.5	0.02	Krajinovic *et al*., 2002 [73]
IKZF1	Important transcription factor expressed in a hematopoietic stem cell that regulates cell proliferation and differentiation during haematopoiesis, particularly in lymphoid cell lineage, and the adaptive immune system	rs4132601 T/G	170/ 150	Tunisian	4.07	0.027	Mahjoub *et al*., 2019 [74]
ARID5B	Transcriptional regulation and differentiation of B lymphocyte progenitors.	rs10821936 C > T	128/ 242	Egyptian	1.45	0.011	Mosaad *et al*., 2019 [75]
CDKN2A	Capable of inducing cell cycle arrest in G1 and G2 phases	rs3731246 G>C	136/ 153	Yemeni	2.01	0.047	Al-absi *et al*., 2017
FOXP3	Transcriptional regulator which is crucial for the	rs3761548	128/124	Egyptian	3.07	<0.01	El-Maadawy

	development and inhibitory function of regulatory T-cells						*et al*., 2022 [84]
FLT3	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine FLT3LG and regulates differentiation, proliferation and survival of hematopoietic progenitor cells	rs35958982	155/155	Pakistan	2.30	=0.005	Khalid *et al*., 2019 [85]
PAX5	Transcription factor that plays an essential role in commitment of lymphoid progenitors to the B-lymphocyte lineage	rs3780135	155/155	Pakistan	2.17	=0.0001	Khalid *et al*., 2019 [85]
FLT3	Tyrosine-protein kinase that acts as cell-surface receptor for the cytokine FLT3LG and regulates differentiation, proliferation and survival of hematopoietic progenitor cells	rs12430881	155/155	Pakistan	1.15	=0.006	Khalid *et al*., 2019 [85]
CYP2D6	A cytochrome P450 monooxygenase involved in the metabolism of fatty acids, steroids and retinoids	CYP2D6*4	200/200	Kashmir (India)	27.43	<0.0001	Nida *et al*., 2017 [86]
MTHFR	Catalyses the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, a co-substrate for homocysteine remethylation to methionine	C677T	95/255	North India	1.73	=0.02	Sood *et al*., 2010
GST01	Involved in the metabolism of xenobiotics and carcinogens	GSTO1*A140D	96/99	Egypt	2.22	=0.028	Yassa *et al*., 2021 [102]
NQO1	This protein's enzymatic activity prevents the one electron reduction of quinones that results in the production of radical species.	C609T	2264/3798	-	1.46	<0.05	Li, & Zhou, 2014 [82]
CYP2E1	Cytochrome P450 proteins are monooxygenases which catalyse many reactions involved in drug metabolism and synthesis of cholesterol, steroids and other lipids	CYP2E1*5	174/337	Canada	1.7	<0.05	Krajinovic *et al*., 2002 [73]

Table 2: GWAS uncovered diverse candidate genes

Region	Gene	Function	Risk allele	Or	95% ci (text)	p-value
7p15.3	SP4	Transcription factor that can bind to the GC promoter region of photoreceptor signal transduction system.	rs2390536-A	1.18	[1.11-1.24]	2.00E-08
8q24.21	CCDC26	It is an RNA Gene, and is affiliated with the lncRNA class	rs4617118-G	1.28	[1.19-1.37]	2.00E-12
17q21.1	GSDMB	Precursor of a pore-forming protein that acts as a downstream mediator of granzyme-mediated cell death	rs2290400-T	1.17	[1.11-1.23]	1.00E-09
7p12.2	IKZF1	This gene encodes a transcription factor that belongs to the family of zinc-finger DNA-binding proteins associated with chromatin remodelling.	rs11978267-A	1.43	-	2.00E-29
9p21.3	CDKN2B	This gene encodes a cyclin-dependent kinase inhibitor, which forms a complex with CDK4 or CDK6, and prevents the activation of the CDK kinases	rs2069426-A	1.35	-	4.00E-09
10p12.2	PIP4K2A	The protein encoded by this gene is one of a family of enzymes capable of catalyzing the phosphorylation of phosphatidylinositol-5-phosphate on the fourth hydroxyl of the myo-inositol ring to form phosphatidylinositol-5,4-bisphosphate.	Rs4748813-T	1.35	-	3.00E-20
10q21.2	ARID5B	Transcription coactivator that binds to the 5'-AATA[CT]-3' core sequence and plays a key role in adipogenesis and liver development	rs7089424-T	1.64	-	2.00E-62
14q11.2	CEBPE/ SLC7A8	C/EBP are DNA-binding proteins that recognize two different motifs: the CCAAT homology common to many promoters and the enhanced core homology common to many enhancers.	rs2239633-T	1.26	-	7.00E-13
10q26.13	LHPP	Phosphatase that hydrolyzes imidodiphosphate, 3-phosphohistidine and 6-phospholysine.	rs3740540-C	1.16		6.00E-06
12q24.22	MAP1LC3B2	Predicted to enable microtubule binding activity and ubiquitin protein ligase binding activity.	rs2089222-A	2.26	[1.60-3.0]	8.00E-08
1q43	RYR2	Encoded protein is one of the components of a calcium channel	rs7554607-A	1.49	[1.20-1.70]	2.00E-06
3q26.32	KCNMB2	Regulatory subunit of the calcium activated potassium KCNMA1 (maxiK) channel	rs9290663-T	1.58	[1.20-1.90]	6.00E-06
12p13.32	TIGAR	This gene is regulated as part of the p53 tumor suppressor pathway and encodes a protein with sequence similarity to the bisphosphate domain of the glycolytic enzyme that degrades fructose-2, 6-bisphosphate.	rs10849033-G	2.55	[1.60-3.80]	9.00E-06
19q13.31	ZNF230	Predicted to be involved in regulation of transcription by RNA polymerase II.	rs2191566-G	1.52	[1.20-1.70]	4.00E-07
1p31.1	ST6GALNAC3	Sialyltransferase activity	rs10873876-T	1.55	[1.20-1.80]	4.00E-06
1q31.3	CFHR1/ CFHR4	This gene encodes a secreted protein belonging to the complement	rs6428370-G	1.43	[1.20-1.60]	7.00E-06

		factor H protein family and involved in complement regulation.				
18p11.32	METTL4	Enables RNA methyltransferase activity and site-specific DNA-methyltransferase (adenine-specific) activity.	rs1879352-C	1.53	[1.20-1.80]	9.00E-06
10p11.21	PARD3	Adapter protein involved in asymmetrical cell division and cell polarization processes	rs563507-A	2.00	[1.40-2.70]	9.00E-06
2q36.1	KCNE4	voltage-gated potassium channel activity and responsible for diverse functions include regulating neurotransmitter release, heart rate, insulin secretion, neuronal excitability, epithelial electrolyte transport, smooth muscle contraction, and cell volume.	rs12621643-T	1.48	[1.20-1.70]	3.00E-06

(GWAS Catalog (ebi. ac. Uk &Gene Cards)

Conclusion

In conclusion, several factors are proved through several studies that lead to childhood ALL and includes certain environmental factors, chemical exposures, inherited syndromes, molecular and genetic changes, paternal or maternal smoking / Tobacco / alcohol consumption, and family history of leukemia or lymphoma. To this end, it is suggested that precautions should be taken by the parents not to get exposed to certain environmental factors like radiation, chemicals, pesticides, smoking, and tobacco, alcohol at least before planning a child and even during pregnancy.

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Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

SD, & AS downloaded the literature, SD, SS, AS& MY filtered the literatures, SD & AS drafted the manuscript, RKP, MY, AB& KM edited the manuscript& picture, PK finalize the review.

References

1. Arora RS, Arora B. Acute leukemia in children: A review of the current Indian data. South Asian Journal of Cancer. 2016;5(3):155-160.
2. Asthana S, Labani S, Mehrana S, Bakhshi S. Incidence of childhood leukemia and lymphoma in India. Pediatric Hematology Oncology Journal. 2018 Dec 1;3(4):115-20.
3. Shukla S, Chhikara A, Bundela T, Sharma S, Chandra J. Clinical, morphological and immunophenotypical findings in acute leukemia: A study from a tertiary care hospital. Iranian Journal of Pediatric Hematology and Oncology. 2020 Jul 10;10(3):136-43.
4. Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood cancer journal. 2017;7(6):e577. https://doi.org/10.1038/bcj.2017.53
5. Fircanis S, Merriam P, Khan N, Castillo JJ. The relation between cigarette smoking and risk of acute myeloid leukemia: an updated meta-analysis of epidemiological studies. American Journal of Hematology. 2014;89(8):E125-32.
6. Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. Journal of oncology. 2011 Jan 1.
7. Shu XO, Ross JA, Pendergrass TW, Reaman GH, Lampkin B, Robison LL. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. JNCI: Journal of the National Cancer Institute. 1996 Jan 3;88(1):24-31.
8. Chang ET, Smedby KE, Hjalgrim H, Porwit-MacDonald A, Roos G, Glimelius B, *et al*. Family history of hematopoietic malignancy and risk of lymphoma. Journal of the National Cancer Institute. 2005 Oct 5;97(19):1466-74.
9. Fraga CG, Motchnik PA, Wyrobek AJ, *et al*. Smoking and low antioxidant levels increa.se oxidative damage to sperm DNA. Mutat Res. 1996;3511;199-203.
10. Shi Q, Ko E, Barclay L, *et al*. Cigarette smoking and aneuploidy in human sperm MolReprod Dev. 2001;59:417-21.
11. Milne E, Greenop KR, Scott RJ, de Klerk NH, Bower C, Ashton LJ, *et al*. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors. Cancer Causes & Control. 2013 Feb;24(2):391-402.
12. Pluth JM, Ramsey MJ, Tucker JD. Role of maternal exposures and newborn genotypes on newborn chromosome aberration frequencies. Mutat Res. 2000;465:101-11.
13. John EM, Savitz DA, Sandler DP. Prenatal exposure to parents' smoking and childhood cancer. Am J Epidemiol. 1991;133:123-32.
14. Metayer C, Petridou E, Aranguré JM, Roman E, Schüz J, Magnani C, *et al*. Parental tobacco smoking and acute myeloid leukemia: the childhood leukemia international consortium. American journal of epidemiology. 2016 Aug 15;184(4):261-73.
15. Pang D, McNally R, Birch JM. Parental smoking and childhood cancer: results from the United Kingdom Childhood Cancer Study. Br J Cancer. 2003;88:373-81.
16. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer Epidemiology and Prevention Biomarkers. 2010 May 1;19(5):1238-60.
17. Skibola CF, Slager SL, Berndt SI, Lightfoot T, Sampson JN, Morton LM, *et al*. Medical history, lifestyle, family history, and occupational risk factors for adult acute lymphocytic leukemia: the Inter Lymph Non-Hodgkin Lymphoma Subtypes Project. Journal of the National Cancer Institute Monographs. 2014 Aug 1;2014(48):125-9.

18. BoiceJr JD, Miller RW. Childhood and adult cancer after intrauterine exposure to ionizing radiation. Teratology. 1999 Apr;59(4):227-33.
19. Wakeford R. The risk of childhood leukaemia following exposure to ionizing radiation-a review. Journal of Radiological Protection. 2013 Jan 7;33(1):1.
20. Berrington de Gonzalez A, Salotti JA, McHugh K, *et al*. Relationship between Pediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. British journal of cancer. 2016;114(4):388-94.
21. Moysich KB, Menezes RJ, Michalek AM. Chernobyl-related ionising radiation exposure and cancer risk: an epidemiological review. The Lancet Oncology. 2002 May 1;3(5):269-79.
22. Ha M HyoungjuneIm, Lee M, Kim HJ, Kim BC, Gimm YM, Pack JK. Radio-Frequency Radiation Exposure from AM Radio Transmitters and Childhood Leukemia and Brain Cancer. American Journal of Epidemiology. 2007;166(3):270-279.
23. Calvente I, Fernandez MF, Villalba J, Olea N, Nuñez MI. Exposure to electromagnetic fields (non-ionizing radiation) and its relationship with childhood leukemia: a systematic review. Science of the total environment. 2010 Jul 15;408(16):3062-9.
24. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, *et al*. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer research. 2001 Mar 3;61(6):2542-6.
25. Pelkonen O, Terron A, Hernandez AF, Menendez P, Bennekou SH. Chemical exposure and infant leukaemia: development of an adverse outcome pathway (AOP) for aetiology and risk assessment research. Archives of toxicology. 2017 Aug 1;91(8):2763-80.
26. Zhang L, Steinmaus C, Eastmond DA, Xin XK, Smith MT. Formaldehyde exposure and leukemia: a new meta-analysis and potential mechanisms. Mutation Research/Reviews in Mutation Research. 2009 Mar 1; 681(2-3):150-68.
27. Ferreira JD, Couto AC, Pombo-de-Oliveira MS, Koifman S. Brazilian Collaborative Study Group of Infant Acute Leukemia. In utero pesticide exposure and leukemia in Brazilian children< 2 years of age. Environmental health perspectives. 2013 Feb;121(2):269-75.
28. Moore PS, Chang Y. Why do viruses cause cancer? Highlights of the first century of human tumour virology. Nature reviews cancer. 2010;10(12):878-889.
29. Koskenvuo M, Möttönen M, Rahiala J, Saarinen-Pihkala UM, Riikonen P, Waris M, *et al*. Respiratory viral infections in children with leukemia. The Pediatric infectious disease journal. 2008 Nov 1;27(11):974-80.
30. Wood DJ, Corbitt G. Viral infections in childhood leukemia. Journal of Infectious Diseases. 1985 Aug 1;152(2):266-73.
31. Couch RB, Englund JA. Respiratory viral infections in immunocompetent and immunocompromised persons. The American journal of medicine. 1997 Mar 17;102(3):2-9.
32. Rauscher GH, Sandler DP, Poole C, Pankow J, Mitchell B, Bloomfield CD, *et al*. Family history of cancer and incidence of acute leukemia in adults. American Journal of Epidemiology. 2002;156(6):517-26.
33. Kuijten RR, Strom SS, Rorke LB, Boesel CP, Buckley JD, Meadows AT, *et al*. Family history of cancer and seizures in young children with brain tumors: a report from the Childrens Cancer Group (United States and Canada). Cancer Causes & Control. 1993 Sep;4(5):455-64.
34. Anderson LA, Pfeiffer RM, Rapkin JS, Gridley G, Mellemkjaer L, Hemminki K, *et al*. Survival patterns among lymphoma patients with a family history of lymphoma. Journal of clinical oncology. 2008 Oct 20;26(30):4958.
35. Cuttner J. Increased incidence of hematologic malignancies in first-degree relatives of patients with chronic lymphocytic leukemia. Cancer Investigation. 1992;10:103
36. Chiu BC, Weisenburger DD, Zahm SH, Cantor KP, Gapstur SM, Holmes F, *et al*. Agricultural pesticide use, familial cancer, and risk of non-Hodgkin lymphoma. Cancer Epidemiol Biomarkers Prev. 2004;13: 525-31.
37. Laurent AP, Kotecha RS, Malinge S. Gain of chromosome 21 in hematological malignancies: lessons from studying leukemia in children with Down syndrome. Leukemia. 2020 Aug;34(8):1984-99.
38. Lejeune J. Mongolism; a chromosomal disease (trisomy). Bull Acad Natl Med. 1959;143:256-65.
39. Dutzmann CM, Spix C, Popp I, Kaiser M, Erdmann F, Erlacher M, *et al*. Cancer in children with Fanconi anemia and Ataxia-Telangiectasia-a nationwide register-based cohort study in Germany. Journal of Clinical Oncology. 2022 Jan 1;40(1):32-9.
40. Brown AL, De Smith AJ, Gant VU, Yang W, Scheurer ME, Walsh KM, *et al*. Inherited genetic susceptibility to acute lymphoblastic leukemia in Down syndrome. Blood. 2019;134(15):1227-37.
41. Skoczen S, Stepien K, Mlynarski W, Centkowski P, Kwiecinska K, Korostynski M, *et al*. Genetic Signature of Acute Lymphoblastic Leukemia and Netherton Syndrome Co-incidence-First Report in the Literature. Frontiers in oncology. 2020 Jan 17;9:1477.
42. Kratz CP, Jongmans MC, Cavé H, Wimmer K, Behjati S, Guerrini-Rousseau L, *et al*. Predisposition to cancer in children and adolescents. The lancet child & adolescent health. 2021 Feb 1;5(2):142-54.
43. Fujita TC, Sousa-Pereira N, Amarante MK, Watanabe MA. Acute lymphoid leukemia etiopathogenesis. Molecular Biology Reports. 2021 Jan;48(1):817-22.
44. Bloom M, Maciaszek JL, Clark ME, Pui CH, Nichols KE. Recent advances in genetic predisposition to pediatric acute lymphoblastic leukemia. Expert review of hematology. 2020 Jan 2;13(1):55-70.
45. Tebbi CK. Etiology of acute leukemia: A review. Cancers. 2021;1(9):2256.
46. Moorman AV, Harrison CJ, Buck GA, 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 Apr 15;109(8):3189-97.

47. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008;371(9617):1030-1043.
48. Soverini S, Colarossi S, Gnani A, Castagnetti F, Rosti G, Bosi C, *et al*. Resistance to dasatinib in Philadelphia-positive leukemia patients and the presence or the selection of mutations at residues 315 and 317 in the BCR-ABL kinase domain. Haematological. 2007 Mar 1;92(3):401-4.
49. Pui CH, Roberts KG, Yang JJ, Mullighan CG. Philadelphia chromosome-like acute lymphoblastic leukemia. Clin Lymphoma Myeloma Leuk. 2017 17:464-70.
Doi: 10.1016/j.clml.2017.03.299
50. Mellentin JD, Smith SD, Cleary ML. lyl-1, a novel gene altered by chromosomal translocation in T cell leukemia, codes for a protein with a helix-loop-helix DNA binding motif. Cell. 1989;58(1):77-83
51. Mullighan CG, Collins-Underwood JR, Phillips LA, Loudin MG, Liu W, Zhang J, *et al*. Rearrangement of CRLF2 in B-progenitor–and Down syndrome–associated acute lymphoblastic leukemia. Nature genetics. 2009 Nov;41(11):1243-6.
52. Rieder H, Schnittger S, Bodenstein H, Schwonzen M, Wörmann B, Berkovic D, *et al*. dic (9; 20): A new recurrent chromosome abnormality in adult acute lymphoblastic leukemia. Genes, Chromosomes and Cancer. 1995 May;13(1):54-61.
53. Clark R, Byatt SA, Bennett CF, Bra M, Martineau M, Moorman AV, *et al*. Monosomy 20 as a pointer to dicentric (9; 20) in acute lymphoblastic leukemia. Leukemia. 2000 Feb;14(2):241-6.
54. Lejman M, Chałupnik A, Chilimoniuk Z, Dobosz M. Genetic biomarkers and their clinical implications in B-cell acute lymphoblastic leukemia in children. International Journal of Molecular Sciences. 2022 Mar 2;23(5):2755.
55. Ferrando AA, *et al*. Gene expression signatures define novel oncogenic pathways in T cell acute lymphoblastic leukemia. Cancer Cell. 2002;1(1):75-87.
56. Roberts KG, Li Y, Payne-Turner D, Harvey RC, Yang YL, Pei D, *et al*. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014 371:1005-15.
Doi: 10.1056/NEJMoa1403088
57. Schultz KR, Carroll A, Heerema NA, Bowman WP, Aledo A, Slayton WB, *et al*. Long-term follow-up of imatinib in pediatric Philadelphia chromosome-positive acute lymphoblastic leukemia: Children's Oncology Group study AALL0031. Leukemia. 2014 Jul;28(7):1467-71.
58. Chalandon Y, Thomas X, Hayette S, Cayuela JM, Abbal C, Huguet F, *et al*. Randomized study of reduced-intensity chemotherapy combined with imatinib in adults with Ph-positive acute lymphoblastic leukemia. Blood, the Journal of the American Society of Hematology. 2015 Jun 11;125(24):3711-9.
59. Zhang J, Ding L, Holmfeldt L, Wu G, Heatley SL, Payne-Turner D, *et al*. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012 Jan;481(7380):157-63.
60. Tawana K, Drazer MW, Churpek JE. Universal genetic testing for inherited susceptibility in children and adults with myelodysplastic syndrome and acute myeloid leukemia: are we there yet? Leukemia. 2018;32:1482-1492.
61. Treviño LR, Yang W, French D, Hunger SP, Carroll WL, Devidas M, *et al*. Germline genomic variants associated with childhood acute lymphoblastic leukemia. Nature genetics. 2009 Sep;41(9):1001-5.
62. Furuhata A, Murakami M, Ito H, Gao S, Yoshida K, Sobue S, *et al*. GATA-1 and GATA-2 binding to 3′ enhancer of WT1 gene is essential for its transcription in acute leukemia and solid tumor cell lines. Leukemia. 2009 Jul;23(7):1270-7.
63. Al-Khreisat MJ, Hussain FA, Abdelfattah AM, Almotiri A, Al-Sanabra OM, Johan MF. The Role of NOTCH1, GATA3, and c-MYC in T cell Non-Hodgkin Lymphomas. Cancers. 2022 Jun 4;14(11):2799.
64. Sudershan A, Mahajan K, Singh K, Dhar MK, Kumar P. The complexities of migraine: A debate among migraine researchers: A review. Clinical Neurology and Neurosurgery. 2022;214:107136.
65. Van Vlierberghe P, Ferrando A. The molecular basis of T cell acute lymphoblastic leukemia. The Journal of clinical investigation. 2012 Oct 1;122(10):3398-406.
66. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics 2000. CA Cancer journal clinic. 2000;50:7-34.
67. Brondum J, Shu XO, Steinbuch M, *et al*. Parental cigarette smoking and the risk of acute leukemia in children. Cancer. 1999;85:1380-8.
68. Infante-Rivard C, Weichenthal S. Pesticides and childhood cancer: an update of Zahm and Ward's 1998 review. Journal of Toxicology and Environmental Health, Part B. 2007;10(1-2):81-99.
69. Rashed WM, Hammad AM, Saad AM, Shohdy KS. MicroRNA as a diagnostic biomarker in childhood acute lymphoblastic leukemia; systematic review, meta-analysis and recommendations. Critical reviews in oncology/ hematology. 2019;1(136):70-78.
70. Belson M, Beverely K and Holmes A. Risk factors for Acute Leukemia in children: A review. Environmental Health Perspectives. 2007;115(1):138-145.
71. Bener A, Denic S, Al-Mazrouei M. Consanguinity and family history of cancer in children with leukemia and lymphomas. Cancer. 2001;92(1):1-6.
72. Rudant J, Menegaux F, Leverger G, Baruchel A, Nelken B, Bertrand Y, *et al*. Household exposure to pesticides and risk of childhood hematopoietic malignancies: the ESCALE study (SFCE). Environmental Health Perspectives. 2007;115(12):1787-1793.
73. Krajinovic M, Labuda D, Sinnett D. Glutathione S-transferase P1 genetic polymorphisms and susceptibility to childhood acute lymphoblastic leukaemia. Pharmacogenetics and Genomics. 2002;12 (8):655-658.
74. Mahjoub S, Chayeb V, Zitouni H, Ghali RM, Regaieg H, Almawi WY, *et al*. IKZF1 genetic variants rs4132601 and rs11978267 and acute lymphoblastic leukemia risk in Tunisian children: a case-control study. BMC Medical Genetics. 2019;20(1):1-7.
75. Mosaad YM, Khashaba M, Darwish A, Darwish M, Elwassefy M, Abdelmabood S, *et al*. ARID5B rs10821936 and rs10994982 gene polymorphisms and acute lymphoblastic leukemia: relation to disease susceptibility and outcome. Pediatric hematology and oncology. 2019;36(6):365-375.

76. Al-Absi B, Razif MF, Noor SM, Saif-Ali R, Aqlan M, Salem SD, *et al*. Contributions of IKZF1, DDC, CDKN2A, CEBPE, and LMO1 gene polymorphisms to acute lymphoblastic leukemia in a Yemeni population. Genetic testing and molecular biomarkers. 2017;21(10):592-599.
77. Latino-Martel P, Chan DS, Druesne-Pecollo N, Barrandon E, Hercberg S, Norat T. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(5):1238-1260. https://doi.org/10.1158/1055-9965.EPI-09-1110
78. Panagopoulou P, Skalkidou A, Marcotte E, Erdmann F, Ma X, Heck JE, *et al*. NARECHEM-ST group. Parental age and the risk of childhood acute myeloid leukemia: results from the Childhood Leukemia International Consortium. Cancer epidemiology. 2019;59:158-165. https://doi.org/10.1016/j.canep.2019.01.022
79. Leuraud K, Richardson DB, Cardis E, Daniels RD, Gillies M, O'Hagan JA, *et al*. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. The Lancet. Haematology. 2015;2(7):e276-e281. https://doi.org/10.1016/S2352-3026(15)00094-0
80. Merks JHM, Caron HN, Hennekam RC. High incidence of malformation syndromes in a series of 1,073 children with cancer. American journal of medical genetics Part A. 2005;134(2):132-143.
81. Krajinovic M, Sinnett H, Richer C, Labuda D, Sinnett D. Role of NQO1, MPO and CYP2E1 genetic polymorphisms in the susceptibility to childhood acute lymphoblastic leukemia. International journal of cancer. 2002;97(2):230-236.
82. Li C, Zhou Y. Association between NQO1 C609T polymorphism and acute lymphoblastic leukemia risk: evidence from an updated meta-analysis based on 17 case–control studies. Journal of cancer research and clinical oncology. 2014;140(6):873-881.
83. Yassa ME, Arnaout HH, Botros SK, Obaid EN, Mahmoud WM, Morgan DS. The role of glutathione S-transferase omega gene polymorphisms in childhood acute lymphoblastic leukemia: a case-control study. Egyptian Journal of Medical Human Genetics. 2021;22(1):1-10.
84. El-Maadawy EA, Bakry RM, Moussa MM, El-Naby SH, Talaat RM. Genetic variation in FOXP3 and ROR-γ genes in pediatric acute lymphocytic leukemia (ALL) patients: correlation with associated cytokines. Discover Oncology. 2022;13(1):1-16.
85. Khalid A, Aslam S, Ahmed M, Hasnain S, Aslam A. Risk assessment of FLT3 and PAX5 variants in B-acute lymphoblastic leukemia: A case–control study in a Pakistani cohort. Peer J. 2019;7:e7195.
86. Nida S, Javid B, Akbar M, Idrees S, Adil W, Ahmad GB. Gene variants of CYP1A1 and CYP2D6 and the risk of childhood acute lymphoblastic leukaemia; outcome of a case control study from Kashmir, India. Molecular biology research communications. 2017;6(2):77-84.
87. Mohammad Shahid Masroor, Mohammad Salim, Shagufta Parween, Mayuri Singh. Recent trends in the study of Roseoloviruses causing diseases, complications and cancer in human. Int. J Adv. Biochem. Res. 2020;4(2):08-10. DOI: 10.33545/26174693.2020.v4.i2a.48
88. Campos-Sanchez E, Toboso-Navasa A, Romero-Camarero I, Barajas-Diego M, Sanchez-García I, Cobaleda C. Acute lymphoblastic leukemia and developmental biology: a crucial interrelationship. Cell cycle (Georgetown, Tex.). 2011;10(20):3473-3486. https://doi.org/10.4161/cc.10.20.17779
89. Belson M, Kingsley B, Holmes A. Risk factors for acute leukemia in children: A review. Environmental health perspectives. 2007;115(1):138-145. https://doi.org/10.1289/ehp.9023
90. Hernández AF, Menéndez P. Linking Pesticide Exposure with Pediatric Leukemia: Potential Underlying Mechanisms. International journal of molecular sciences. 2016;17(4):461. https://doi.org/10.3390/ijms17040461
91. Tong J, Qin L, Cao Y, Li J, Zhang J, Nie J, *et al*. Environmental radon exposure and childhood leukemia. Journal of toxicology and environmental health. Part B, Critical reviews. 2012;15(5):332-347. https://doi.org/10.1080/10937404.2012.689555
92. Altieri A, Castro F, Bermejo JL, Hemminki K. Number of siblings and the risk of lymphoma, leukemia, and myeloma by histopathology. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2006;15(7):1281-1286. https://doi.org/10.1158/1055-9965.EPI-06-0087
93. Ferreira JD, Couto AC, Pombo-de-Oliveira MS, Koifman S. Brazilian Collaborative Study Group of Infant Acute Leukemia. Pregnancy, maternal tobacco smoking, and early age leukemia in Brazil. Frontiers in oncology. 2012;2:151. https://doi.org/10.3389/fonc.2012.00151
94. Cao Y, Lu J, Lu J. Paternal Smoking before Conception and During Pregnancy Is Associated With an Increased Risk of Childhood Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis of 17 Case-Control Studies. Journal of pediatric hematology/oncology. 2020;42(1):32-40. https://doi.org/10.1097/MPH.0000000000001657
95. Kakaje A, Alhalabi MM, Ghareeb A, Karam B, Mansour B, Zahra B, *et al*. Interactions of Consanguinity and Number of Siblings with Childhood Acute Lymphoblastic Leukemia. Bio Med research international, 2020, 7919310. https://doi.org/10.1155/2020/7919310
96. Anderson LA, Tavilla A, Brenner H, Luttmann S, Navarro C, Gavin AT, *et al*. EUROCARE-5 Working Group: (2015). Survival for Oesophageal, stomach and small intestine cancers in Europe 1999-2007: Results from EUROCARE-5. European Journal of cancer (Oxford, England: 1990). 2020;51(15):2144-2157. https://doi.org/10.1016/j.ejca.2015.07.026
97. Sharma S, Kelly TK, Jones PA. Epigenetics in cancer. Carcinogenesis. 2010;31(1):27-36. https://doi.org/10.1093/carcin/bgp220

98. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-674.
99. Anderson CA, Gentile DA, Buckley KE. Violent video game effects on children and adolescents: Theory, research, and public policy. Oxford University Press; 2007 Jan 11.
100. Chang DT, Honick AS, Reynolds IJ. Mitochondrial trafficking to synapses in cultured primary cortical neurons. Journal of Neuroscience. 2006 Jun 28;26(26):7035-45.
101. Bloom N, Van Reenen J, Williams H. A toolkit of policies to promote innovation. Journal of economic perspectives. 2019 Aug;33(3):163-84. https://doi.org/10.1016/j.cell.2011.02.013
102. Sood S, Das R, Trehan A, Ahluwalia J, Sachdeva MU, Varma N, *et al*. Methylenetetrahydrofolate Reductase gene polymorphisms: association with risk for pediatric acute lymphoblastic leukemia in north Indians. Leukemia & lymphoma. 2010;51(5):928-932.