Journal Pre-proofs

Review

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PII: S0378-1119(20)30074-3
DOI: https://doi.org/10.1016/j.gene.2020.144405
Reference: GENE 144405

To appear in: *Gene Gene*

Received Date: 6 November 2019
Accepted Date: 27 January 2020

Please cite this article as: C. Dieter, E. Dutra Lourenco, N. Emerim Lemos, Association of long non-coding RNA and leukemia: a systematic review, *Gene Gene* (2020), doi: https://doi.org/10.1016/j.gene.2020.144405

Association of long non-coding RNA and leukemia: a systematic review

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Running title: *lncRNAs and leukemia*

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Abstract

Introduction: Long non-coding RNAs (lncRNAs) are RNA molecules that structurally resemble mRNA but do not encode proteins. Studies have been associated this class of non-coding RNA with the development of several disease, among them the different types of leukemia. However, the results are contradictory. Thus, we performed a systematic review of the literature available in order to better understand the involvement of lncRNAs in the development of leukemia. **Materials and Methods:** Pubmed and Embase databases were used to identify all studies that evaluated the expression of one or more lncRNA between human samples (peripheral blood, bone marrow) with leukemia (cases) and without leukemia (controls). **Results:** A total of 3675 articles were found in the databases, and after exclusion of articles that did not meet the eligibility criteria, 86 articles were included in this systematic review. In the 86 included studies, 3927 lncRNAs were differentially expressed between cases and controls. Among these, 110 lncRNAs were reported as being altered in samples from at least 2 studies and only 16 of them in ≥ 3 studies, which were selected for further evaluation. Of these, 12 lncRNAs were consistently dysregulated between cases and controls **(**CCAT1, CCDC26, CRNDE, HOTAIR, KCNQ5IT1, LINC00265, MALAT1, PVT1, SNHG5,TUG1: increased in cases, MEG3 and NEAT1: decreased in cases) in human samples of patients with some type of leukemia. **Conclusion:** Our data demonstrate that 12 lncRNAs are dysregulated in leukemia.

Keywords: leukemia; lncRNAs; systematic review; epigenetics.

Introduction

Leukemia is a type of cancer that affects the blood and bone marrow and is characterized by the uncontrolled production and accumulation of blood cells (1). According to American Cancer Society (2), cancer the second leading cause of deaths among children, adolescents and young adults younger than 20 years, and leukemia is the main type of cancer that affect children. In addition, 381,774 people are living with or in remission from leukemia in the US (2). Radiation exposure, viral infections, ethnicity, gender and genetic mutations are some of the risk factors of leukemia (1). However, more studies are necessary to better understand the development and the pathogenesis of the different types of leukemia.

In this context, epigenetic factors, such as non-coding RNAs (ncRNA), have been associated with leukemia development. NcRNAs are a group of regulatory RNAs that are not translated into protein (3). NcRNAs longer than 200 nucleotides are classified as long non-coding RNAs (lncRNAs). LncRNAs are located in nucleus, where they can act as molecular scaffolds, help in alternative splicing or modify chromatin structures. In addition, there are some lncRNAs that have functions in cytoplasm, such as modulating translation, promoting or inhibiting mRNA degradation, and acting as miRNAs sponges (4).

Dysregulated expression of this lncRNAs is highly associated with human diseases, including the different types of leukemia [review in (5-7)]. Take into account that a large number of studies have demonstrated the association of lncRNA expression with leukemia and that many findings are contradictory, the aim of this study is clarify the involvement of lncRNAs in the pathogenesis of leukemia, performing a systemic review of the literature on the subject.

Materials and Methods

Search strategy and eligibility of studies

This study was designed and reported in accordance with current guidelines (8, 9), and its protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/ PROSPERO), with the number of CRD42019126586. PubMed and Embase databases were searched to find all articles that investigated lncRNAs expressions in human leukemia samples. The following medical subject headings (MeSH) were used: ("Leukemia" OR "Leukemia, Lymphoid" OR "Leukemia, Myeloid") AND ("RNA, long noncoding" OR "untranslated RNA"). The search was restricted to English, Spanish or Portuguese language papers and was finished on June, 2019. References from all articles were also manually checked in order to identify other relevant citations.

Articles that evaluated lncRNAs expressions in leukemia patients (cases) and subjects without leukemia (control groups) were included in this systematic review. Studies that did not have an appropriate control group were excluded. Two researchers (C.D. and N.E.L.) independently reviewed titles and abstracts of all articles retrieved to evaluate whether they were eligible for inclusion in this study.

Data extraction and quality assessment of each study.

Results were independently collected by two investigators (C.D. and N.E.L.) using a standardized abstraction form (8), and consensus was sought in all extracted items. When consensus could not be achieved, differences in data extraction were decided by reading the original publication or by consulting a third reviewer (E.D.L.). Information extracted from each study was as follow: 1) characteristics of studies and samples; 2)

information regarding lncRNAs expression, which included method used for quantification, tissue analyzed, and number of lncRNAs investigated; and 3) lncRNA expressions in each study group.

Two investigators (C.D. and N.E.L.) evaluated the quality of each eligible study using the Newcastle-Ottawa Scale (NOS) (10). The NOS contains eight items divided into three dimensions: selection, comparability, and exposure. For each item, a sequence of answer options is provided. A star scoring system is used to allow a semi-quantitative evaluation of paper quality, such that the highest quality studies are given a maximum of one star for each item, with exception of the item related to comparability, which allows two stars to be given. Therefore, the final NOS score varies from 0 to 9 stars.

Results

Literature search, characteristics of the eligible studies and quality assessment

Figure 1 shows a flowchart illustrating the strategy used to select studies form inclusion in this systematic review. A total of 3675 possible relevant citations were retrieved from Pubmed and Embase, and 3236 of them were excluded during the review of title and abstracts. Following full text analyses, only 86 articles fulfilled the eligibility criteria and were included in this review (11-96) [Figure 1 near here]. **Table 1** shows the main characteristics of these articles [Table 1 near here]. Regarding Al-Dewik et al, 2017 (11) study, we could include only the information that were in the abstract. Additionally, a few articles with array analysis do not informed the name of all lncRNAs dysregulated in cases compared to controls, because of this, for these articles we included in our systematic review only the information that were in the full-text (16, 22, 53, 64). Besides these, few articles analyzed the expression of lncRNAs more than once in the

same patients, but in different regions of the chromosome where this lncRNA is found, as shown in **Supplementary Table 1** (26, 34) and for later analysis, we considered these lncRNAs only once. In relation to the articles that analyzed the same lncRNAs in different tissue types, we included these results separately, taking into account that the expression of epigenetic factors can be tissue specify (55).

Most of the included studies comprised patients with acute myeloid leukemia (AML) (61%), 14% of the articles have patients with acute lymphoid leukemia (ALL), 10% with chronic myeloid leukemia (CML), 6% with chronic lymphoid leukemia (CLL), 5% of the studies analyzed AML and ALL patients, 1% analyzed CML and ALL patients, 1% lymphoid leukemia (LL), 1% juvenile myelomonocytic leukemia (JMML) and 1% do not informed the leukemia type. Leukemia diagnostic was performed according to French-American British (FAB) or World Health Organization (WHO) classification.

The number of lncRNAs differentially expressed between groups in included studies ranged from 1 to 6069. The number of samples sizes analyzed varying from 6 to 248. Regarding the tissues analyzed, 55% of the articles evaluated lncRNAs expression in bone marrow samples, 30% in blood samples, 8% in bone marrow and blood samples, and 7% of the articles do not described in which sample they analyzed the lncRNAs.

Supplementary Table 2 shows the quality of each individual study, assessed using the NOS scale. The highest quality studies were awarded nine stars. In general, most studies were considered as having good or moderate quality selection, comparability and exposure. Seventeen of the studies scored less than four stars, 47% of the studies had five or six stars and 33% of the studies had seven, eight or nine stars.

Most of the studies with four or less stars are abstracts from congress, and thus have little information.

Dysregulated lncrRNAs in leukemia-related tissues

A total of 3927 lncRNAs were reported differentially expressed between case and controls, 110 of them in at least two studies and 16 of them were significantly different in three or more studies and were selection for further evaluations (**Supplementary Table 1**). LncRNAs that were concordant results in more than 75% of the studies in which they were analyzed were considered consistently dysregulated in leukemia. Thus, as demonstrate in **Table 2**, 10 lncRNAs were consistently upregulated in leukemia cases compared to controls, and 2 lncRNAs were downregulated [Table 2 near here]. Some lncRNAs were upregulated in cases from one study, while were downregulated in cases from another study, such as H19 and IGF2. These contradictory results may be due to differences in tissue types, or type of leukemia that was analyzed (**Supplementary Table 1**).

Discussion

Besides the genetics factors, such as polymorphisms, associated with the pathogenesis of leukemia, nowadays epigenetics factors have been studying in the context of this disease. Regarding to these epigenetic factors, lncRNAs still have contradictory results and more studies are necessary to better understand its involvement in the pathogenesis of leukemia. Because of this, we performed a systematic review where they were included 86 articles and our results show the consistently dysregulation of 12 lncRNAs in leukemia patients.

Regarding the lncRNAs that were downregulated, MEG3 (*maternally expressed gene 3*) was the most studied, analyzed in seven articles with AML, CML or ALL patients (26, 34, 35, 37-39, 59). This lncRNA is located on chromosome 14q32 and expressed in normal tissues (97). Studies have been reported the loss of MEG3 in various human cancers, including breast, bladder, and liver cancers (98, 99). In leukemia patients MEG3 expression was downregulated in bone marrow and serum samples compared the control group (26, 34, 35, 37-39, 59). Li J. *et al.,* reported the downregulated of MEG3 in leukemia patients and cells lines and suggested that this lncRNAs could be a biomarker for leukemia (59). Additionally, downregulation of this lncRNA may promote the proliferation of tumor cells, since MEG3 can promote the binding of tumor suppressor gene P53 to target (98-100). LncRNA NEAT1 (*nuclear paraspeckle assembly transcript 1*) is located in chromosome 11, act as a tumor suppressor by promoting leucocyte differentiation (61) and was also downregulated in leukemia patients (23, 60, 61, 64, 84). Zeng C, *et al.* demonstrated NEAT1 downregulation in acute promyelocytic leukemia patients (AML-M3) when compare to controls (61), as well as Zhao C. *et a.l,* in primary AML and THP-1 cells (64). Moreover, the expression of this lncRNA was suppresses in HL-60, Jurkat , and K562 leukemia cell lines, in comparison with peripheral white blood cells and the overexpression ameliorated multi drug resistance phenotype induced by cytotoxic compounds (23). In CML cells, NEAT1 expression is also decreased and NEAT1 silencing enhanced imatinib-induced apoptosis (60). In contrast with these results, in different types of solid tumor, such as lung cancer, colorectal cancer and hepatocellular carcinoma, this lncRNA is very upregulated [review in (101)].

Ten lncRNAs were consistently upregulated in leukemia patients compared control group. LncRNA HOTAIR (*HOX transcript antisense RNA*) was reported to be

upregulated in peripheral blood or bone marrow samples of CML, ALL or AML patients in nine articles (11, 20, 24, 27, 55, 56, 63, 75, 89). This lncRNA is located within the *HOMEOBOX C* (*HOXC*) gene cluster on chromosome 12q13.13 and have been show dysregulated in several types of cancers (102). In addition, lncRNA HOTAIR act in several hallmarks of cancer, such as cellular proliferation, inhibition of apoptosis, genomic instability, angiogenesis, invasion and metastasis (103-105). In hematologic malignancies, HOTAIR has been suggested a potential biomarker of poor prognosis and potential therapeutic target for AML treatment, since its expression was correlated with clinical-pathological prognostic stratification in AML (27, 55, 104). Moreover, silencing of HOTAIR inhibited cell growth, induced apoptosis, and decreased number of colony-forming cells in AML (104); and the knockdown of HOTAIR reduced activation of the PI3K/Akt pathway (104, 106). In CML, HOTAIR seems to be involved in acquired resistance to imatinib being upregulated in K562-imatinib-resistant cells and in patients with high expression of *MRP1* and demonstrated opposite effects when HOTAIR knockdowned, decreasing *MRP1* expression and consequently increased sensitivity to imatinib treatment (106).

LncRNA MALAT1 (*metastasis-associated lung adenocarcinoma transcript 1)* is also reported consistently upregulated in leukemia patients compared the control individuals (15, 30, 34, 60, 70, 84). MALAT1 is a nuclear lncRNAs and abundantly expressed in normal tissues (107). Also, this lncRNA seems to be involved in several types of cancers, by mediating proliferation, invasion, metastasis and regulating PI3K-Akt, MAPK, WNT, and NF-κB pathways [review in (108)]. In K562 cells, MALAT1 was reported to be upregulated when compared with peripheral blood cells from healthy donors and the MALAT1 silencing inhibited the proliferation and arrested cell cycle by target miR-328 (109). Huang JL. *et al*, demonstrated the upregulation of MALAT1

expression in acute monocytic leukemia patients (AML-M5) compare with the healthy group (30). In cellular experiments with U-937 and THP-1 cells (M5 cell lines), MALAT1 knockdown decreased M5 cells proliferation, inhibited cell cycle progression and increased apoptosis, suggesting the association between MALAT1 high expression and poor prognosis in M5 patients (30).

In addition to lncRNAs HOTAIR and MALAT1, the expressions of lncRNAs CRNDE (*colorectal neoplasia differentially expressed*) (26, 33, 34, 54), PVT1 (*plasmacytoma variant translocation 1*) (29, 32, 34, 62, 74), SNHG5 (*small nucleolar RNA host gene 5*) (26, 28, 34, 95) and TUG1 (*taurine up-regulated 1*) (34, 36, 50, 80, 86) were also increased in leukemia patients compare the respectively control group. Regarding lncRNA CRNDE, Wang Y. *et al*, demonstrated its upregulation in AML patients, especially in AML-M4 and M5, when compared with controls (54). *In vitro*, lncRNA CRNDE promote U937 cell line proliferation, cell cycle and suppressed apoptosis (54). Additionally, it was reported upregulated in bone marrow from AML patients and in primary ALL cells (26, 34). LncRNA PVT1 is located on chromosome 8q24, has been shown to be dysregulated in many cancers types and associated with cancer tumorigenesis, tumor stage and poor survival (110-115). When analyzed in bone marrow and peripheral blood mononuclear cells (PBMCs) from ALL and AML patients, PVT1 was reported to be upregulated compared healthy individuals (29, 32, 34, 62). Studies performed in ALL cell lines also demonstrated the high expression of PVT1 in comparison to the control group (116-118). Furthermore, PVT1 knockdown in Jurkat cells increased apoptosis rate, cause G0/G1 arrest during the cell cycle, reduced proliferation and stability of c-Myc protein (116).

LncRNA SGNH5 was upregulated in CML patients when compared with healthy controls and in K562-imatinib-resistant cells when compared to normal K562

cells (28). The authors also demonstrated that SNHG5 overexpression increased imatinib resistance in K562 cells, and SNHG5 knockdown could reduce imatinib resistance in K562-imatinib-resistant cells (28).Other studies verified that lncRNA SNHG5 expression was higher in AML and ALL patients in comparison of the control groups (26, 34). Regarding the involvement of SNHG5 in other cancer, it was upregulated in melanoma tumor tissue and the downregulation of this lncRNA in melanoma cells could repress proliferation, promoted apoptosis and decreased invasion (119). Moreover, in colorectal cancer cells, SNHG5 seems to be involved in regulation of proliferation, metastasis, migration and inhibition of apoptosis (120). In AML patients, Wang X. *et al* demonstrated that lncRNA TUG1 was upregulated (34, 36, 50) and also reported the association of TUG1 expression with advanced disease and poor prognosis (50). *In vitro*, the authors shown that lncRNA TUG1 induced cell proliferation and decreased apoptosis in AML cells, suggesting its involvement in pathogenesis of AML by mediating cell proliferation and cell apoptosis (50). Furthermore, to act as an oncogene and involved in the development and prognosis of several carcinomas (121-123). In osteosarcoma cells, TUG1 downregulation inhibits proliferation and promotes apoptosis (124). In the same way, in cervical cancer, overexpression of TUG1 promotes cell growth and metastasis by inhibiting miR-138-5p expression (125).

Additionally, lncRNAs CCAT1 (*Colon cancer-associated transcript-1*) (14, 32, 74), CCDC26 (32-34), KCNQ5IT1 (*KCNQ5 intronic transcript 1*) (33, 34, 60) and LINC00265 (34, 81) were also upregulated in leukemia patients in comparison to the control group. LncRNA CCAT1 is located in chromosome 8q24.21, and has been reported upregulated in solid tumors, such as colon cancer, gastric and hepatocellular carcinoma (126-128). In leukemia context, CCAT1 seems to be upregulated (14, 32, 74)

and demonstrated promote cell proliferation and inhibit myeloid cell differentiation by acting as a competing endogenous RNA for miR-155 (14). LncRNA CCD26 was demonstrated upregulated in ALL and AML patients (32-34). Izadifard M. *et al.* shown that this lncRNA was not different between all AML patients and healthy controls, but only when they analyzed AML-M2 and AML-M4/M5 patients in comparison to the control group (32). In *in vitro* study, Hirano T. *et al.* demonstrated that CCD26 knockdown in K562 cells results in transcriptionally-altered expression of several genes, including activation of KIT, and prolonged cell survival under low or no serum conditions (129). Because of these results, the authors suggest that CCDC26 could controls growth of myeloid leukemia cells through regulation of KIT expression (129).

LncRNA LINC00265 is a new identified lncRNA in human cancers and is upregulated in lung adenocarcinoma (130). In leukemia, LINC00265 expression was higher in bone marrow and serum from AML patients (34, 81). Additionally, Ma L. *et al.* suggest that this lncRNA is an independent prognosis factor for AML and demonstrated that LINC00265 knockdown suppressed AML cell lines proliferation, migration and invasion and promoted apoptosis by PI3K-Akt pathway (81). Regarding the lncRNA KCNQ5-IT1, it was only reported in array studies and was higher expressed in ALL, AML and CML patients in comparison to control group (33, 34, 60). Although it is dysregulated in leukemia, little is known about the function of this lncRNA and more studies are necessary to better understand the involvement of KCNQ5-IT1 in this disease.

This systematic review has a few limitations. First, few studies, especially with RNAseq and array, do not inform the names of lncRNA different expressed between cases and controls and if the lncRNA is up- or downregulated. Second, we cannot excluded the possibility that we loss same information, since there is no official

nomenclature for lncRNAs. Moreover, the use of different techniques to quantify and analyze lncRNA expression profiles makes impossible to perform a quantitative analysis of the data (meta-analysis). In addition, most studies did not provide raw expression values, only if lncRNA was significantly up- or downregulated.

In conclusion, our systematic review shown that 12 lncRNAs are consistently dysregulated in leukemia patients compared with controls. LncRNAs MEG3 and NEAT1 were downregulated, while lncRNAs CCAT1, CCDC26, CRNDE, HOTAIR, KCNQ5IT1, LINC00265, MALAT1, PVT1, SNHG5 and TUG1 were upregulated. All of the lncRNAs seems to act in pathways involved in cancer pathogenesis and appears to have the potential to be used as therapeutic targets or may to be use as a biomarker for leukemia. Although, more studies are necessary to better understand the exact involvement of these non-coding RNAs in leukemia development.

Declarations

Ethics approval and consent to participate

N/A

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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Supplementary material list

Supplementary Table 1. LncRNAs analyzed in the studies included in the systematic review between leukemia patients and controls.

Supplementary Table 2. Newcastle-Ottawa quality assessment scale for the studies included in the systematic review.

Table 1. Characteristics of studies included in the systematic review.

First author, year (Ref)	Study design	Leukemia classification	Tissue	Method	Increased	Decreased	Observations
Ahmadi, A. 2018 (70)	30 CLL patients; 30 healthy controls	CLL	PBMNCs	qPCR	1	0	
Al-Dewik, NI. 2017* (11)	15 CML patients: 5 in chronic phase, 5 with complete remission, 5 in accelerated phase; 5 healthy controls	CML	Peripheral blood	qPCR	4	2	
Asadi, M. 2018* (71)	ALL patients; healthy controls	ALL	BMMNCs	qPCR	0	1	
Azari, I. 2018* (72)	25 AML patients; healthy controls	AML	Peripheral blood	qPCR	0	0	
Bisio, V. 2017* (12)	132 children with de novo AM; healthy controls	AML	Bone marrow	qPCR	1	0	BALR-2 expression was not correlated with any specific genetic abnormality
Bock, O. 2003 (67)	11 CML patients; 33 healthy controls	CML	Bone marrow	qPCR	0	1	
	12 chronic myelomonocytic leukemia patients; 33 healthy controls	CMML	Bone marrow	qPCR	0	1	
Cao, L. 2016 (13)	22 children with AML; 20 healthy controls	AML	BMMNCs	Microarray and qPCR	51	85	
Chen, L. 2016 (14)	60 AML patients; 60 healthy controls	AML	PBMNCs	qPCR	1	0	CCAT1 expression was difference between cases and controls and in the subtypes of AML-M4 and M5
Chen, S. 2018 (15)	70 de novo AML patients; 11 healthy controls	AML	BMMNCs	qPCR	1	0	MALAT1 was upregulated in AML patients with cytogenetic abnormalities [t(9;11)(p22;q23), t(6;9) (p23;q34), inv(3) (q21q26.2), t(3;3) (q21;q26.2),

							t(1;22)(p13;q13), t(9;22)(q34;q11)] *vs* healthy controls.
Cheng, H. 2017 (16)	6 AML patients, 6 healthy controls	AML	BMMNCs	Microarray	562	449	
	6 ALL patients; 6 healthy controls	ALL	BMMNCs	Microarray	3310	2759	
Congrains-Castillo, A. 2019 (73)	28 AML patients; 15 healthy controls	AML	BMMNCs	qPCR	0	1	
Corrocher, FA. 2015 (17)	11 AML patients; 7 healthy controls	AML	CD34+ cells from bone marrow	qPCR	0	0	
Diaz-Beya, 2015 (18)	214 de novo AML patients; healthy controls	AML	Bone marrow and peripheral blood	qPCR	-	-	No difference was found between cases and controls, only APL patients had decreased expression of HOTARM1 and patients with AML t (6,9) presented higher expression of HOTARM1, both compared to other AML patients
Eizadifard, M. 2017* (19)	76 AML patients; 18 healthy controls	AML	Bone marrow	qPCR	0	1	Significant IRAIN downregulation was observed in all FAB types except for the M3.
El Khazragy, N. 2019 (74)	70 de novo AML patients; 20 healthy controls	AML	PBMNCs	qPCR	2	0	LncRNAs CCAT1 and PVT1 were also upregulated in t(8;21) positive AML patients compare to t(8;21) negative AML patients.
El Khazragy, N. 2019b (75)	70 AML patients: 30 with 12p chromosomal abnormalities and 40 cytogenetic negative or other chromosomal abnormality; 20 healthy controls	AML	Bone marrow	qPCR	1	0	Hotair was also upregulated in AML patients with 12p chromosomal abnormalities when compare to cytogenetic negative or other chromosomal abnormality patients.

Fallah, H. 2018* (76)	AML patients; healthy controls	AML	Peripheral blood	qPCR	0	0	
Fallah, P. 2018 (20)	40 B-ALL patients; 15 healthy controls	ALL	Bone marrow	qPCR	1	0	
Feng, Y. 2018 (21)	151 AML patients; iron deficiency anemia	AML	BMMNCs	Array	37	112	
Fernando, TR. 2015 (22)	118 B-ALL patients; 19 healthy controls	B-ALL	PBMCs	Microarray and qPCR	-	-	Four lncRNAs were validated (Upregulated: BALR-1, BALR-2, BALR-6 and LINC00958)
Gan, S. 2019 (77)	40 AML patients; 25 healthy controls	AML	Bone marrow	qPCR	1	0	
	23 ALL patients; 25 healthy controls	ALL	Bone marrow	qPCR	1	0	
Gao, C. 2016 (23)	36 patients; 15 healthy controls	-	Peripheral white blood cells	qPCR	0	1	
Gao, S. 2018 (24)	10 AML patients; 8 healthy controls	AML	CD34+ cells from bone marrow and from cord blood	qPCR	1	0	
Garding, A. 2013 (25)	34 CLL patients; 20 healthy controls	CLL	CD19+ cells from PBMCs	qPCR	2	1	
Garitano-Trojaola, A. 2018 (26)	4 ALL patients; 3 healthy controls	ALL	Primary ALL cells and peripheral blood	Microarray and qPCR	25	46	
Guan, X. 2019 (78)	146 de novo AML patients; 73 healthy controls	AML	Bone marrow	qPCR	1	0	
Hao, S. 2015 (27)	34 AML patients: 21 with de novo AML, 13 with complete remission; 16 iron deficiency anemia patients	AML	Bone marrow	qPCR	1	0	HOTAIR was upregulated in de novo AML patients compared to the complete remission group and the iron deficiency anemia patients
He, B. 2017 (28)	40 CML patients; 20 healthy controls	CML	Peripheral blood cells	qPCR	1	0	

Hofmans, M. 2018 (79)	44 juvenile myelomonocytic leukemia; 7 helathy controls	JMML	Bone marrow	Array	15	285	
Hu, J. 2018 (29)	20 AML patients; 40 healthy controls	AML	Bone marrow	qPCR	0	0	
	48 ALL patients; 40 controls	ALL	Bone marrow	qPCR	1	0	
Huang, JL. 2017 (30)	95 AML patients; 37 healthy controls	AML	BMMNCs	qPCR	1	0	MALAT1 was increased in AML-M5 patients when compared with the control group and non-AML-M5 patients
Isin, M. 2014 (31)	68 CLL patients; 40 healthy controls	CLL	Blood	qPCR	0	1	
Izadifard, M. 2018 (32)	86 de novo AML patients; 40 healthy controls	AML	BMMNCs	qPCR	3	0	PVT1 was upregulated in AML-M3 patients *vs* controls; CCDC26 was upregulated in AML-M2 and AML-M4/M5 *vs* controls; and CCAT1 was upregulated in AML-M4/M5 *vs* controls
Lajoie, M. 2017 (33)	56 children with pre-B ALL; 3 healthy controls	ALL	White blood cells from bone marrow and peripheral blood	RNAseq			
Lei, L. 2018 (34)	6 AML patients; 2 healthy controls	AML	Bone marrow	Array and qPCR	1657	959	
Li, J. 2018 (35)	57 AML patients; 57 healthy controls	AML	Peripheral blood	qPCR	0	1	
Li, J. 2018b (95)	194 AML patients; 61 healthy controls	AML	Bone marrow and serum	qPCR	1	0	
Li, Q. 2019 (36)	36 AML patients; 23 healthy controls	AML	Bone marrow	qPCR	1	0	
Li, S. 2019 (96)	10 children with ALL; 4 healthy controls	ALL	Peripheral blood	qPCR	2	0	

	20 children with ALL; 10 healthy controls	ALL	Bone marrow	qPCR	2	0	
Li, Z. 2018 (37)	40 CML patients: 20 in chronic phase, 10 in accelerated phase and 10 in blast phase; 10 healthy controls	CML	Bone marrow	qPCR	0	1	MEG3 was downregulated in CML patients in accelerated phase and blast phase *vs* controls and chronic phase.
Li, ZY. 2018 (38)	60 CML patients; 10 healthy controls	CML	Bone marrow	qPCR	0	1	
Luo, W. 2018 (80)	73 AML patients; 37 healthy controls	AML	Bone marrow	qPCR	1	0	
Lyu, Y. 2017 (39)	42 AML patients; 15 healthy controls	AML	CD34+ cells from bone marrow	qPCR	0	1	
Ma, L. 2018 (81)	135 AML patients; 35 healthy controls	AML	Bone marrow and serum	qPCR	1	0	
Miller, CR. 2017 (40)	6 CLL patients; 5 healthy controls	CLL	B cells from peripheral blood	Microarray and qPCR	-	-	Eight lncRNAs were validated between CLL and healthy controls (Downrgulated: LncRNA3145, lncRNA6588, lncRNA3901, lncRNAtreRNA; Upregulated: lncRNA3967, AK126772, AK000998, lncREL1.1)
Morenos, L. 2014 (41)	26 children with AML; 30 healthy controls	AML	Bone marrow	qPCR	0	1	
Neddermeyer, A. 2018* (82)	AML patients; healthy controls	AML	Bone marrow	RNAseq	-	-	LncRNA xloc-091701 was upregulated in AML patients.
Papaioannou, D. 2018* (83)	AML patients; healthy controls	AML	Bone marrow	qPCR	1	0	HOXB-AS3 was also higher in NPM1 mutant AML patients compare to AML wild type patients.
Pashaiefar, H. 2018 (42)	64 de novo non M3 AML patients; 51 healthy controls	AML	BMMNCs	qPCR	0	1	

Pouyanrad, S. 2019 (84)	64 ALL patients: 46 newly cases and 18 relapsed cases; 30 healthy controls	ALL	Bone marrow	qPCR	2	0	Neat1 was upregulated in all ALL patients *vs.* controls, while Malat1 was upregulates in relapsed cases *vs.* controls.
Qi, X. 2019 (85)	35 AML patients: 9 – M1, 8 – M2, 6 – M3 and 12 –M5; 21 healthy controls	AML	-	Array and qPCR	0	1	
Qin, J. 2018 (86)	236 de novo AML patients; 118 healthy controls	AML	Bone marrow	qPCR	1	0	
Sajjadi, E. 2018 (43)	30 CML patients; 30 healthy controls	CML	Peripheral blood	qPCR	1	0	
Sayad, A. 2017 (68)	25 AML patients; 50 controls	AML	Peripheral blood	qPCR	0	0	
Sayad, A. 2018 (44)	25 de novo AML patients; 50 controls	AML	Peripheral blood	qPCR	0	0	AML subtypes: M0 – M5
Shi, X. 2019 (87)	62 de novo AML patients; 4 healthy controls	AML	Bone marrow	Array and qPCR	1	0	ZEB2-AS1 was dysregulated in the array analysis.
Song, Z. 2018 (45)	6 T- LL patients; 2 healthy controls	LL	PBMCs	qPCR	1	0	
Sun, C. 2017 (46)	96 CML patients; 96 healthy controls	CML	-	qPCR	1	0	
Sun, J. 2014 (47)	34 AML patients; 10 healthy controls	AML	Bone marrow	qPCR	0	0	IRAIN was upregulated in AML low risk patients *vs* AML high risk patients. There was no difference between case and control group.
Sun, LY. 2018 (69)	109 AML patients; 14 healthy controls	AML	-	qPCR	1	0	
Taheri, M. 2018* (88)	De novo AML patients; healthy controls	AML	Peripheral blood	qPCR	0	0	
Wang, H. 2014 (48)	14 AML patients; 5 healthy controls	AML	Bone marrow	qPCR	1	0	

Wang, Q. 2017 (49)	30 B-ALL patients; 30 healthy controls	ALL	Bone marrow	qPCR	1	0	
Wang, SL. 2019 (89)	90 AML patients; 30 healthy controls	AML	Bone marrow	qPCR	1	0	
Wang, X. 2018 (50)	186 AML patients; 62 healthy controls	AML	Bone marrow	qPCR	1	0	
Wang, X. 2019 (90)	5 BCR-ABL ALL patients; 5 healthy controls	ALL	Peripheral blood lymphocytes	qPCR	3	0	
Wang, Y. 2018a (51)	153 AML patients; 54 healthy controls	AML	Bone marrow and serum	qPCR	1	0	AML subtypes: M0 – M7
Wang, Y. 2015 (52)	20 children with T-ALL; 10 healthy controls	ALL	Bone marrow	qPCR	1	0	
Wang, Y. 2018b (53)	3 T-ALL patients; 3 healthy controls	ALL	Bone marrow	Microarray	204	128	
	100 children with T-ALL; 100 healthy controls	ALL	CD4+ T cells from bone marrow	qPCR	1	0	
Wang, Y. 2018c (54)	81 de novo AML patients; 35 healthy controls	AML	Bone marrow	qPCR	1	0	
Wu, S. 2015 (55)	85 AML patients; 40 healthy controls	AML	Peripheral blood and BMMNCs	qPCR	1	0	
Xing, CY. 2015 (56)	136 AML patients; healthy controls	AML	BMMNCs	qPCR	1	0	
Yang, JR. 2019 (91)	30 CML patients; 10 healthy controls	CML	Bone marrow	qPCR	1	0	
Yang, MY. 2011 (57)	89 AML patients: 67 with normal karyotype, 22 with abnormal karyotype; 39 healthy controls	AML	-	qPCR	6	0	IGF2, H19, SLC22a3 and COPG2 were upregulated in AML patients with normal karyotype *vs* control group; IGF2, H19, AMPD3 and GABRB3 were upregulated in AML patients with abnormal

							karyotype *vs* control group.
Yang, T. 2018 (58)	34 ALL patients; 43 healthy controls	ALL	Peripheral blood – T cells	qPCR	1	0	
Yao, H. 2017 (59)	26 AML patients; 20 healthy controls	AML	-	qPCR	0	1	
Zeng, C. 2014 (61)	31 APL patients; 12 healthy controls	AML	Primary APL cells and granulocytes	qPCR	0	2	
Zeng, C. 2018 (60)	26 CML patients; 12 healthy controls	CML	Peripheral blood	RNAseq and qPCR	200	177	
	28 T-ALL patients; 21 controls	ALL	Peripheral blood	qPCR	0	2	
Zeng, C. 2015 (62)	28 APL patients; 12 healthy controls	AML	PBMCs	qPCR	1	0	
Zhang, X. 2019 (92)	33 AML patients; 15 healthy controls	AML	Bone marrow	qPCR	1	0	
Zhang, Y. 2019 (93)	66 AML patients; 18 healthy controls	AML	-	qPCR	1	0	
Zhang, YY. 2016 (63)	73 AML patients; 80 healthy controls	AML	BMMNCs	qPCR	1	0	HOTAIR was upregulated in AML-M5 patients *vs* control group
	23 ALL patients; 80 healthy controls	ALL	BMMNCs	qPCR	0	0	
Zhao, C. 2018 (64)	3 AML patients; 3 healthy controls	AML	Primary AML cells and PBMNCs	Microarray and PCR	51	56	
Zhao, TF. 2017 (65)	107 AML patients; 53 healthy controls	AML	Bone marrow	qPCR	1	0	H19 was upregulated in AML-M2 patients *vs* healthy controls
Zhou, JD. 2018 (66)	85 CML patients; 36 healthy controls	CML	BMMNCs	qPCR	1	0	

Zhuang, MF. 2019 (94)	80 AML patients: 5 – M0, 6 – M1, 11 – M2, 12 – M3, 5 – M4, 31 – M5 and 10 – M6; 24 healthy controls	AML	Bone marrow	qPCR	1	0	HOTTIP was upregulated in M5 AML patients in comparison with the controls.

*Abstract from congress. ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; BMMCs: bone marrow-derived mononuclear cells; CML: chronic myeloid leukemia; JMML: juvenile myelomonocytic leukemia; PBMCs: Peripheral blood mononuclear cells.

Table 2. LncRNAs consistently different expressed in leukemia patients and analyzed in at least three articles.

LncRNA	First author, year	Tissue	Change of expression	Leukemia Type
CCAT1	El Khazragy, N. 2019	PBMNCs	Up	AML
	Chen, L. 2016	PBMNCs	Up	AML
	Izadifard, M. 2018	BMMNCs	Up	AML
CCDC26	Izadifard, M. 2018	BMMNCs	Up	AML
	Lei, L. 2018	Bone marrow	Up	AML
	Lajoie, M. 2017	Bone marrow and peripheral blood	Up	ALL
CRNDE	Lajoie, M. 2017	Bone marrow and peripheral blood	Up	ALL
	Garitano-Trajaola, A. 2018	Primary ALL cells	Up	ALL
	Lei, L. 2018	Bone marrow	Up	AML
	Wang, Y. 2018b	Bone marrow	Up	AML
HOTAIR	Al-Dewik, NI. 2017	Peripheral blood	Up	CML
	El Khazragy, N. 2019b	Bone marrow	Up	AML
	Fallah, P. 2018	Bone marrow	Up	ALL
	Gao, S. 2018	Bone marrow	Up	AML
	Hao, S. 2015	Bone marrow	Up	AML
	Wang, SL. 2019	Bone marrow	Up	AML
	Wu, S. 2015	Peripheral blood	Up	AML
	Wu, S. 2015	BMMCs	Up	AML
	Xing, CY, 2015	BMMCs	Up	AML
	Zhang, YY. 2016	BMMCs	Up	AML
KCNQ5-IT1	Lajoie, M. 2017	Bone marrow and peripheral blood	Up	ALL
	Lei, L. 2018	Bone marrow	Up	AML

	Zeng, C. 2018	Peripheral blood	Up	CML
LINC00265	Lei, L. 2018	Bone marrow	Down	AML
	Lei, L. 2018	Bone marrow	Up	AML
	Ma, L. 2018	Bone marrow	Up	AML
	Ma, L. 2018	Serum	Up	AML
MALAT1	Ahmadi, A. 2018	PBMNCs	Up	CLL
	Chen, S. 2018	BMMCs	Up	AML
	Huang, JL. 2017	BMMCs	Up	AML
	Lei, L. 2018	Bone marrow	Up	AML
	Pouyanrad, S. 2019	Bone marrow	Up	ALL
	Zeng, C. 2018	Peripheral blood	Down	CML
MEG3	Garitano-Trojaola, A. 2018	Primary ALL cells	Down	ALL
	Lei, L. 2018	Bone marrow	Down	AML
	Li, J. 2018	Peripheral blood	Down	AML
	Li, Z. 2018	Bone marrow	Down	CML
	Li, ZY. 2018	Bone marrow	Down	CML
	Lyu, Y. 2017	CD34+ cells from bone marrow	Down	AML
	Yao, H. 2017	Bone marrow	Down	AML
NEAT1*	Gao, C. 2016	Peripheral white blood cells	Down	Leukemia
	Pouyanrad, S. 2019	Bone marrow	Up	ALL
	Zeng, C. 2014	Primary APL cells and granulocytes	Down	AML
	Zeng, C. 2014†	PBMNCs	Up	AML
	Zeng, C. 2018	Peripheral blood	Down	ALL
	Zeng, C. 2018	Peripheral blood	Down	CML

	Zeng, C. 2018†	Peripheral blood	Down	ALL
	Zhao, C. 2018	Primary AML cells and PBMNCs	Down	AML
PVT1	El Khazragy, N. 2019	PBMNCs	Up	AML
	Hu, J. 2018	Bone marrow	Up	ALL
	Izadiford, M. 2018	BMMCs	Up	AML
	Lei, L. 2018	Bone marrow	Up	AML
	Zeng, C. 2015	PBMNCs	Up	AML
SNHG5	Garitano-Trajaola, A. 2018	Primary ALL cells	Up	ALL
	He, B. 2017	PBMNCs	Up	CML
	Lei, L. 2018	Bone marrow	Up	AML
	Li, J. 2018b	Serum	Up	AML
	Li, J. 2018b	Bone marrow	Up	AML
TUG1	Lei, L. 2018	Bone marrow	Up	AML
	Li, Q. 2019	Bone marrow	Up	AML
	Luo, W. 2018	Bone marrow	Up	AML
	Qin, J. 2018	Bone marrow	Up	AML
	Wang, X. 2018	Bone marrow	Up	AML

ALL: acute lymphoid leukemia; AML: acute myeloid leukemia; BMMCs: bone marrow-derived mononuclear cells; CML: chronic myeloid leukemia; PBMCs: Peripheral blood mononuclear cells. *Some articles have analyzed two NEAT1 variants: NEAT1_1 and NEAT1_2 (†).

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Figure 1. Flowchart illustrating the search strategy used to identify association studies of lncRNAs expression and leukemia for inclusion in the systematic review.

Abbreviations

ALL: acute lymphoid leukemia

AML: acute myeloid leukemia

BBMC: bone marrow mononuclear cell

CLL: chronic lymphoid leukemia

CML: chronic myeloid leukemia

FAB: French American Bristish

JMML: juvenile myelomonocytic leukemia

LncRNA: long non-coding RNA

MESH: medical subject heading

NcRNA: non-coding RNA

NOS: New Castle-Ottawa Scale

PBMC: peripheral blood mononuclear cell

WHO: World Health Organization

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: