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Original article

A Study of Association between miRNA-146a Polymorphism and Acute Lymphoblastic Leukemia in Children

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Abstract:

Background: Acute lymphoblastic leukemia (ALL) is the most common type of pediatric hematopoietic leukemia in children, accounting for 30-35% of all pediatric cancers. Abnormal miRNA expression has been reported to be related to cancers and other diseases , miRNA 146a rs2910164 polymorphism has been widely examined in various types of cancers including hematological cancers . **Methods:** This case control study was conducted on 80 children with ALL (group I) who are admitted at Benha University Hospital and Benha Specialist Hospital for Children and 40 healthy children with matched age and sex as controls (group II), we studied the miRNA-146a (rs2910164) polymorphism using Polymerase Chain Reaction-Restriction Fragment-Length Polymorphism (PCR-RFLP) approach. **Results:** Acute lymphoblastic leukemia (ALL) cases showed significantly higher proportions in GC, CC genotypes and C allele (40% for GG, 38.8% for GC, 21.2% for CC and 59.4% for G and 60.4% for C) (P= 0.023, 0.005, <0.001) when compared to control group ($p<0.05$ for each), with risk to develop ALL (OR>1 for each). **Conclusion:** Our findings suggest that the miR-146a rs2910164 CC genotype was significantly associated with increased childhood ALL susceptibility.

Keywords: Acute lymphoblastic leukemia, miRNA146a , polymorphism

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Introduction

Acute lymphoblastic leukemia (ALL) is cancer of lymphocytes, characterized by over production and accumulation of cancerous immature lymphocytes known as lymphoblasts. These cells are over produced in bone marrow and multiply causing damage and replace normal cells [1].

Acute lymphoblastic leukemia (ALL) is the most common type of pediatric hematopoietic leukemia in children, accounting for 30-35% of all pediatric cancers [2,3]. It represents the most prevalent childhood cancer and the leading cause of cancer mortality in cases under the age of 20. Although a small percentage of ALL cases are linked to inherited genetic syndromes, the underlying genetic mechanisms in many other cases remain unexplained [4].

Multiple factors regulate tumorigenesis and tumor development by altering DNA replication, transcription, and translation. The discovery of these factors, including microRNAs (miRNAs) and long non-coding RNAs, was considered a breakthrough for the early diagnosis and prevention of cancers [5] .

MicroRNAs (micRNAs) are single-stranded noncoding RNAs with a length between 19 and 25 nucleotides that are typically formed from hairpin-shaped precursors [6]. They perform vital roles in the regulation of biological processes, and this occurs through multiple mechanisms, by promoting cell differentiation, maturation, proliferation and apoptosis [5,7].

Deregulated expression by miRNAs could increase the risk of metabolic diseases, such as diabetes and obesity, by disrupting signaling pathways [8]. Also, abnormal miRNA expression has been reported to be related to cancers plus other diseases [9,10] .

MiR-146a has been identified as a modulator of cell differentiation and innate and adaptive immunity. The abnormal expression of miR-146a is frequently observed in human diseases, such as inflammatory disorders and cancers. Previous studies have reported that miR-146a is significantly increased in the peripheral blood samples of pediatric patients with ALL, thus providing valuable insights into potential diagnostic or prognostic biomarkers [11].

The polymorphism of miRNA 146a (rs2910164) involves a G > C nucleotide substitution which causes change from a G:U pair to a C:U mismatch in the stem structure of miRNA 146a precursor that results in a reduced amount of mature miRNA146a [12,13]. Up or down regulation of miRNA-146a is observed in human disorders, such as inflammatory diseases and cancers including breast cancer [14,15] and hepatocellular carcinoma [16] which are reported that *miR146a* G>C polymorphism was associated with increased risk of these cancers . However, another report of meta-analysis suggested an increased risk between *miR146a* (rs2910164) GG genotype and gastric cancer susceptibility [17] .

The aim of this study was to investigate the association between miRNA146a (rs2910164) polymorphism and acute lymphoblastic leukemia in Egyptian children.

Subjects and methods

This case-control study was consists of 120 subjects including 80 childhood ALL patients who were admitted at Benha University Hospital and Benha Specialist Hospital for Children and 40 apparently healthy children as control group . Their age ranged between 3-15 years. The study was performed between November 2020 and September 2021.

Patients were assessed by initial white blood cell count, and confirming diagnosis by bone marrow aspiration, cytogenetic study and Immunophenotypic analysis, also clinical and demographic data including age and sex were retrospectively studied. The study was performed according to the principles approved by

the local ethics committee of Faculty of Medicine of Benha University, Study No: Ms.27.11.2020.

Sample collection : Seven milliliter (ml) of peripheral venous blood were collected from each subject under complete aseptic condition and subsequently divided into 3 parts : 2 ml on K-ethylene diamine tetra-acetic acid (k- EDTA) tube subdivided into two parts one ml for Complete blood count (CBC) and immunophenotyping and the other stored at -20ºC for subsequent DNA extraction For detection of miRNA-146a G\C polymorphism using (PCR-RFLP) technique , 1.6 ml on citrated tube for ESR test and 3 ml on plain tube for clinical chemistry tests (serum AST, ALT , Urea and Creatinine) .

DNA extraction : Genomic DNA was extracted from peripheral whole blood on EDTA tube by QUICK-DNA™ MiniPrep Kit 50 preps (ZYMO RESEARCH) (Epigenetics COMPANY, USA) (Catalog NO : D3024) following the instructions of the manufacturer.

Genotyping of miR146a (G>C) (rs2910164) polymorphism: The single nucleotide polymorphism of miRNA-146a (*rs2910164*) (G>C) was performed by Polymerase Chain Reaction Restriction Fragment Length Polymorphism (PCR-RFLP) analysis. Genotyping of miRNA-146a (*rs2910164*) (G>C) polymorphism was done using forward primer 5ˈ-CATGGGTTGTGTCAGTGT GCAGAGCT-3′ and reverse primer 5ˈ-TGCCTTCTGTCTCCA GTCTTCCAA-3ˈ. Enzymatic amplification was performed by PCR; using2xEasy Taq PCR superMix, specific primers and PCR thermal cycler (Veriti® 96-Well Thermal Cycler (applied biosystems-Model#9902-Singapore) . The amplification of DNA was done in a 25 µl mixture containing 4 µl of template DNA, 1 µl of forward primer, 1 µl of reverse primer, 12.5 µl of 2xEasy Taq® PCR SuperMix and 6.5 µl nuclease free water. The PCR was performed in Thermal cycler (applied biosystems-Model#9902- Singapore).

The PCR protocol was the initial denaturation of 94 ◦C for 5 min followed by 35 cycles of denaturation at 94 ◦C for 30 sec, annealing at 60 ◦C for 15 sec, extension at 72 ◦C for 2 min with a final extension at 72 ◦C for 10 min . The PCR product was detected *by* electrophoresis on 2% agarose gel.

Polymerase Chain Reaction-Restriction Fragment Length Polymorphism (PCR-RFLP): The amplified targeted DNA was digested by *sac1* restriction enzyme (vivantis technologies) (Lot No: 1044F22). The recognition sequence of *sac1* restriction enzyme is:

5`…GAGCT▼ C …3` and 3`…C ▲ TCGAG ... 5`

The miR 146a (rs2910164) G/C polymorphism was detected using 3% agarose gel electrophoresis for 30 minutes at 130 volts and 100 milliamperes and stained with ethidium bromide . The gel was visualized on the filter area of the UV transilluminator for the presence of bands at (147 bp), (122 bp) and (25 bp) (Figure 1), they were identified as three different genotypes as follows :

- One band of (147 bp) indicated the homozygous GG genotype as in lane 5 in the upper half.
- Two bands (122 and 25 bp) indicated the homozygous CC genotype as in lane 6 in the upper half.
- Three bands of (147, 122 , and 25 bp) indicated the heterozygous GC genotype as in lane 5 in the lower half

Statistical analysis*:* The collected data was revised, coded and tabulated using statistical package for Social Science (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). Data were presented and suitable analysis was done according to the type of data obtained for each parameter. A *p* value is considered significant if <0.05 at confidence interval 95%.

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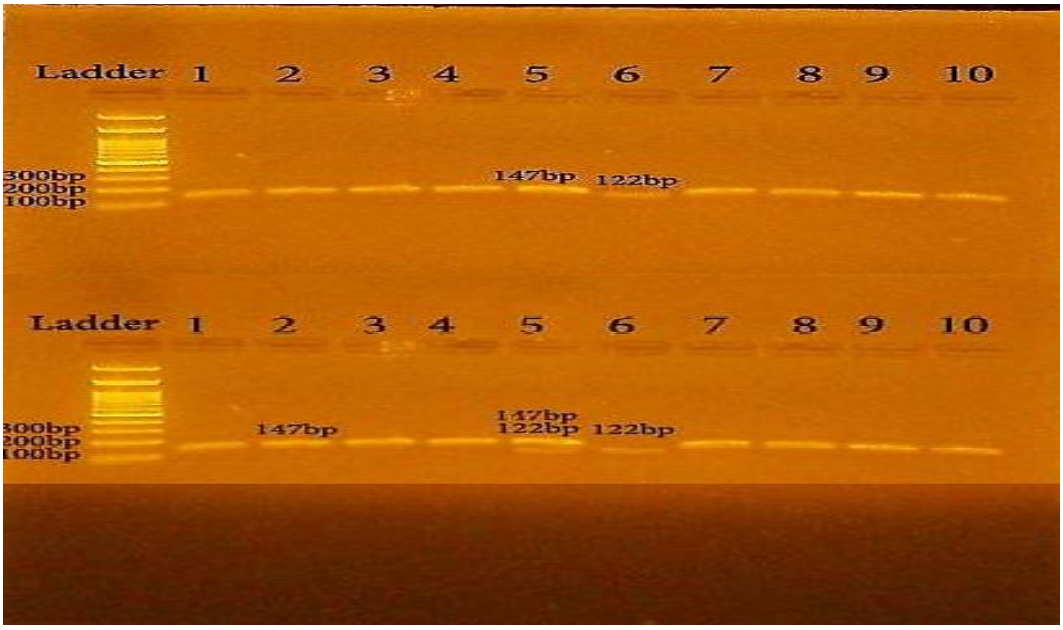

Figure (1): Analysis of miRNA-146a (rs2910164)polymorphism

Results:

The present study included 80 ALL childhood cases and 40 apparently healthy children as control group, the mean age of cases was 5.5 (SD=2.7) years , and for the control was 6.2 (SD=2.8) years .

The genotypic frequencies for miR146a (rs2910164) were determined in the childhood ALL and control groups, and compared with each other and are shown in Table 1, the genotyping considering for miR146a (rs2910164) showed that GC, CC genotypes and C allele were significantly higher proportions in ALL cases when compared to control group ($p<0.05$ for each), with risk to develop ALL (OR>1 for each).

The present study considering GG genotype and G allele as references, GC, CC genotypes and C allele showed significantly higher proportions in ALL cases (40% for GG, 38.8% for GC, 21.2% for CC and 59.4% for G and 60.4% for C) when compared to control group (70% for GG, 25% for GC, 5% for CC and 82.5% for G and 17.5% for C) p value was (P= 0.023 for GC , 0.005for CC and <0.001for C allele) with risk to develop ALL , Our findings suggest that the miR-146a rs2910164 CC genotype was significantly associated with increased childhood ALL susceptibility ($p<0.05$ for each) (OR>1 for each) . (Table 1)

Regression analysis was conducted for prediction of ALL susceptibility using age, gender, total leukocytic count (TLC) and rs2910164 genotypes as confounders. TLC and rs2910164 genotypes were considered predictors of ALL in uni- and multivariable analyses (Table 2).

Table (1). Comparison between rs2910164 genotype and allelic polymorphisms among ALL cases (Group I) compared to controls (Group II)

rs2910164		ALL cases (Group I) N=80		Control (Group II) N= 40		P value	OR (95 % CI)
		N	**%**	**N**	**%**		
Genotype	**GG**	32	40.0	28	70.0	-	**Reference**
	GC	31	38.8	10	25.0	**0.023**	1.841(1.088-3.114**)**
	CC	17	21.2	2	5.0	**0.005**	3.217(1.415-7.314**)**
Allele	**G**	95	59.4	66	82.5	-	**Reference**
	C	65	40.6	14	17.5	**<0.001**	2.010(1.377-2.935**)**

N; number, OR; odds ratio, CI; confidence interval, C; cytosine, G; guanine. Logistic regression analysis was used. Reference genotype and allele according to NCBI. P<0.05 is considered significant; OR<1 is considered protective; OR>1 is considered risky.

Table (2). Regression analysis for prediction of ALL susceptibility.

	Univariable			**Multivariable**		
	p	**OR**	**95% CI**	**P**	**OR**	**95% CI**
Age	0.190	0.946	0.872-1.028			
Gender	0.605	1.130	0.710-1.800			
TLC	**<0.001**	1.167	1.094-1.245	**<0.001**	1.160	1.086-1.238
rs2910164	**0.002**	2.134	1.319-3.453	**0.025**	1.455	1.162-2.776

OR, odds ratio; CI, confidence interval.

Discussion :

Acute lymphoblastic leukemia (ALL) is the most common type of malignancy among children worldwide. The molecular etiology of ALL is not completely understood,studies showed that genetic polymorphisms of some susceptibility genes are associated with the personal susceptibility of childhood ALL [18-22] and it has been reported that microRNAs (miRNAs) may play an important role in the regulation of hematopoiesis [23].

It was showed that small noncoding miRNAs, play important roles in development and cellular processes such as cell proliferation, differentiation, apoptosis and tumorigenesis [15,24] MiRNAs can regulate RNA protein levels; abnormal miRNA expression has been reported to be related to several diseases, including cancers[9,10].

With recent technologies that is used for gene expression analysis, molecular profiling of new microRNAs in childhood ALL, has been reachable [25] .

MiR-146a is a member of microRNAs that is considered to have dual oncogenic and tumor-suppressive roles in cancer because it is overexpressed in pediatric ALL and acute myeloid leukemia (AML), as well as prostate, pancreatic, and breast cancers, and is downregulated in adult AML [26]

The miR146a rs2910164 polymorphism has been widely examined in various types of cancers ,as for childhood leukemia, Previous studies have reported that miR-146a is significantly increased in the peripheral blood samples of pediatric patients with ALL, thus providing valuable insights into potential diagnostic or prognostic biomarkers [11].

Hence the aim of our study was to examine the association between miRNA-146a (rs2910164) polymorphism and childhood ALL in Egypt. In the current

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study, it was suggested that the miR-146a(rs2910164) CC genotype was significantly associated with increased childhood ALL susceptibility in Egyptian children (P< 0.05) .

The genotype frequency of miRNA-146a in our study was 40% for GG , 38.8% for GC and 21.2% for CC in cases compared to 70% for GG , 25% for GC and 5% for CC in control , as for allele it was 59.4% , 40.6% for G and C allele respectively in cases compared to 82.5% for G and 17.5% for C allele in control ,p value was (P= 0.023, 0.005, <0.001) for GC,CC and C allele respctively .

This finding and considering GG genotype and G allele as references, GC, CC genotypes and C allele showed significantly higher proportions in ALL cases when compared to control group and so this study suggested that the miR-146a rs2910164 CC genotype was significantly associated with increased childhood ALL susceptibility . This was in agree with a study done in China reported by ***Liu et al.,*** in 2018 that found that the rs2910164 CC or CG genotype significantly increased the risk of ALL with the results gene frequency of miR146a(rs2910164)GG,GC and CC genotypes in patient group and healthy control group was 16%,44.5%, 39.5% and 29%, 41%, 30%, respectively and the GC/CC genotypes were significantly higher in patient group than those in healthy control group(GG genotype as reference, GC genotype (P=0.037),CC genotype(P=0.012) [27] , Then , in 2019, another study done on Indian children that wasn't in accordance with us and examined the allele frequencies for miR146a SNPs rs2910164 G>C in the patients and controls as they found that there was no significant association was observed between cases and controls (GG was 33.8% for controls and was 38% for cases, CG was 45.1% for cases versu 50 % for controls and CC was 16.9% for cases and 16.2% for controls) , P value was 0.38–1.64 for CG and P value was 0.35–2.43 for CC [28] .

Pei et al., 2020 in a study done in Taiwan found that, the miR146a rs2910164 GG genotype was significantly associated with a decreased susceptibility to childhood ALL , the allele frequencies of miR146a C and G allele were 55.8% and 44.2%, respectively in the control group and 65.6% ,34.4% respectively in patient group, for the genotype it was 42.1% for CC , 47% for CG and 10.9% for GG in patients group [29].

Regarding laboratory findings, our study revealed that ALL cases had significantly higher TLC (mean 35.5 $X10^9$/L) (P < 0.001) , significantly lower RBC (mean 3.7 $X10^{12}$/L) , Hb (mean 10.1 g/dL) and platelet count (mean 160.9$X10^9$/L) (P < 0.001) when compared to control group, this go on line with *Munir et al.,2019* that reported that the basic hematological parameters in cases of ALL were raised WBCs, low Hb and platelet [30], *Kassem et al.;2023* also found significant higher total leukocytic count , significant lower hemoglobin and platelet [31] .

As for clinical findings , we observed that the most common clinical presentation was splenomegaly with 67.5 % then lymphadenopathy with 65% this go in line with Jaime-P´erez et al. who found 63% splenomegaly and lymphadenopathy 57% [32] , while Kakaje et al. found lymphadenopathy was the most common presentation with 82.9% and hepatosplenomegaly 73.9% [33].

In our work, we found no significant association regarding rs2910164 genotype polymorphism with clinical findings, immunophenotyping, and cytogenetics among studied cases.

Regression analysis was conducted in the current study for prediction of ALL susceptibility using age, gender, TLC and rs2910164 genotypes as confounders. TLC and rs2910164 genotypes were considered predictors of ALL in uni- and multivariable analyses.

Conclusion

The current study suggested that the miR-146a rs2910164 CC genotype was significantly associated with increased childhood ALL susceptibility with no significant association regarding rs2910164 genotype polymorphism with age and gender, clinical findings, IPT and cytogenetics among studied cases.

Conflict of interest

None of the contributors declared any conflict of interest

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