

# Clinical significance of HOX11L2 and HOX11 gene expression in T-ALL patients

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## To cite this article:

Said H. Abdu, Doaa Shahin, Mohamed R. El-Shanshory, Hoda A. Salem, Eman A. Amer, Mohamed M. El-Shebeiny. Clinical Significance of HOX11L2 and HOX11 Gene Expression in T-ALL Patients. *Journal of Cancer Treatment and Research*. Vol. 2, No. 3, 2014, pp. 27-32. doi: 10.11648/j.jctr.20140203.12

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**Abstract:** *Objective:* The aim of this study was to determine the prognostic value of two structurally related homeobox genes TLX1/HOX11 and TLX3/HOX11L2 on the clinical outcome of T-ALL patients. *Material and Methods:* The study included 28 newly diagnosed T-ALL patients. HOX11L2 and HOX11 gene expression were detected by real time PCR. Patients received treatment according to the ALL BFM-90 protocol. *Results:* Of 28 patients, 8(28.6%) expressed HOX11L2 and 4(14.3%) expressed HOX11. The overall survival of patients with HOX11L2 expression was lower than of the patients without HOX11L2 expression (log-rank  $P < 0.025$ ). As regards HOX11 expression, a statistically significant difference in clinical outcome was found, where HOX11 expression conferred a prognostic advantage ( $p < 0.001$ ). *Conclusion:* the present study was showed that the outcome of HOX11L2 and HOX11 expression differs, with poor outcome for patients with HOX11L2-expression. Future molecular diagnostics may make use of such leukemia-specific markers as HOX11L2 and HOX11 to detect minimal residual disease.

**Keywords:** HOX11L2, HOX11, Real Time PCR, T-ALL

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## 1. Introduction

T- cell ALL (T-ALL) accounts for 15% of all newly diagnosed pediatric ALL cases and is clinically regarded as a high-risk disease with an unfavorable prognosis<sup>(1,2)</sup>. Treatment of acute lymphoblastic leukemia (ALL) has greatly improved over the last decades, leading to cure in approximately 80-85 %. Recently with the use of modern risk- adjustment multiagent treatment regimens, the five-year event free survival rate became of approximately 70-75%, but still a significant proportion of patients (30%) continue to relapse and they are considered as extremely poor prognosis<sup>(3)</sup>.

A large proportion of cases shows a normal karyotype and recurrent chromosomal abnormalities are detectable only in about 50% of T-ALL using conventional cytogenetic<sup>(4)</sup>. For most of these abnormalities, the T-cell

receptor (TCR)- $\alpha/\delta$  locus (14q11) or TCR- $\beta$  locus (7q34) come close to target genes and activate their ectopic expression<sup>(5,6)</sup>. The introduction of novel technologies has allowed an increasing number of alterations to be obtained by using molecular biology, FISH and gene expression profiling, which have enabled five subgroups to be recognized, i.e. immature/LYL1, TAL, HOX11, HOX11L2, and HOX<sup>(7, 8, 9, 10)</sup>. These genes are frequently targeted during the malignant transformation of T cells by others mechanisms, such as interstitial deletion on chromosome 1 for TAL1/SCL or point mutations for NOTCH1<sup>(11)</sup>. Other translocations not involving TCR loci leading to the formation of specific fusion genes like CALM-AF10, or MLL rearrangements have also been described<sup>(12)</sup>.

Studies have revealed that certain transcriptional factors associated with T-ALL might be useful for prognosis. The most notable examples are two structurally related

homeobox genes TLX1/HOX11 and TLX3/HOX11L2<sup>(13)</sup>. HOX11 is aberrantly expressed in childhood T-ALL as a result of either two chromosomal translocations, t(7;10)(q35;q24) and t(10;14)(q24;q11) which place the HOX11 coding sequence under the transcription control of T-cell receptor regulatory elements. HOX11L2 is involved in a cryptic translocation, t(5;14)(q35;q32), detected only by FISH resulting in its ectopic transcription<sup>(10,14)</sup>.

The aim of this study was to determine the prognostic value of two structurally related homeobox genes TLX1/HOX11 and TLX3/HOX11L2 on the clinical outcome of T-ALL patients.

## 2. Materials and Methods

This study was conducted on 28 patients with T-ALL, attending the haemato-oncology Unit of Pediatric Department and Clinical Oncology Department at Tanta University Hospitals and Tanta Cancer Center, in the period between February 2002 and December 2006. There were 20 males and 8 females, aged from 3 to 13 years. Ten apparently health children of matched age and sex were included in the study as controls. All patients are subjected to complete clinical examination. Diagnosis was based on complete haemogram, BM examination, haematomorphology and immunophenotyping by expression of cytoplasmic and or surface CD3, CD5, CD7, CD1a and negativity for CD19 and MPO according to the European EGIL recommendation<sup>(15)</sup>.

Diagnostics peripheral blood or B.M. samples were taken from 28 patients with T-ALL. Informed consent was obtained from the patients parents in all cases. Follow up of patients were carried out clinically and by blast count in Bone marrow (BM). The white blood cell count with median 102.5 (range from 6-160X10<sup>9</sup>/L), 11 cases with presenting mediastinal mass (39.2%), 5 cases with Central nervous system (CNS) involvement (17.8%), 24 cases with hepatomegaly (85.7%), 25 cases with splenomegaly (89.2%), and 23 cases with lymphadenopathy (82.1%).

Patients were treated according to the ALL BFM-90 Protocol medium-risk group (MRG). The protocol consists of: Induction, followed by consolidation and reinduction in MRG. The number of leukemic blasts in the blood on day 8 was calculated from the absolute leukocyte count. The presence of at least 1000/ $\mu$ L blasts in PB on day 8 was defined as a "prednisone: poor response" (PPR) and the presence of 5% or greater marrow blasts on day 33, shift the treatment to the high risk protocol<sup>(16)</sup>. In high risk group (HRG), the induction followed by intensive reconsolidation (Element HR1, Element HR2, Element HR3) that were repeated 3 times. CNS-directed preventive therapy for HRG patients consisted of 3 doses of intrathecal MTX in induction, and 9 doses of triple-drug intrathecal therapy (MTX, cytarabine, and prednisolone) during intensive consolidation. Preventive CNS irradiation at a dose of 12 Gy was given only in MRG patients at the end of reinduction and in HRG patients after intensive

consolidation. In patients who initially had CNS disease, Cranial radiation therapy (CRT) was administered in age-adapted dosages; thus, patients under 1 year of age received no CRT, patients older than 1 year of age but under 2 years of age received 18 Gy, and patients 2 years of age or older received 24 Gy. These patients also received 2 additional doses of intrathecal MTX in both induction and reinduction, if in the HRG, 1 additional administration of intrathecal triple-drug therapy (MTX, cytarabine, and prednisolone) in each cycle HR-2. In boys with clinically overt testicular involvement, local irradiation (24 Gy) was performed. Other forms of local radiotherapy were not scheduled in protocol ALL-BFM 90. Maintenance therapy was initiated 2 weeks after the end of reinduction or the ninth HR element. The scheduled dose of 6-mercaptopurine was 50 mg/m<sup>2</sup> a day given orally. MTX was given orally at a dose of 20 mg/m<sup>2</sup> once a week, with adjustments in dosage made in accordance with the white blood cell (WBC) count. For all patients, the total duration of therapy was 24 months.

Samples Collection was as follow: BM Aspirates and venous blood samples were collected from each patient under complete aseptic technique. Ten normal peripheral blood lymphocyte RNA were extracted from healthy donors' samples as control group to determine the reference level of TLX1 and TLX3.

RNA was extracted using RNA isolation kit (QIAamp RNA Blood Mini Kit [Qiagen] Cat. No. 52304 according to manufacturers' instructions. (QIAGEN Inc. Valencia • CA. USA) RNA was reversed transcribed from 1  $\mu$ g total RNA in a final volume of 20  $\mu$ l containing reverse transcription polymerase chain reaction (RT-PCR) buffer (1mM each dNTP, 3mM MgCl<sub>2</sub>, 75 mM KCl, 50 mM Tris-HCL pH 8.3) 10U RNA asin (promega Madison, WI), 100 mM dithiothreitol, 100U superscript II (Gibco- BRL, Cergy Pontoise, France), 25  $\mu$ M random hexamers. The expression levels of various target PCR were quantified relative to the expression level of the endogenous housekeeping gene, glyceraldehyde-3-phosphate dehydrogenase (GAPDH), by real time RT-PCR in an Step-One 7400 (PE Applied Biosystems, foster city, CA.USA) as described previously<sup>(18,19)</sup>.

For detection of TLX1/HOX11 expression levels, the forward primer 5'-CTC ACT GGC CTC ACC TT-3' and reverse primer 5'- CTG TGC CAG GCT CTT Ct- 3' were used in combination with the probe 5'- (FAM)- CCT TCA CAC GCC TGC AGA TC- (TAMRA)-3'. For detection of TLX3/HOX 11L2 expression levels, the forward primer 5'- TCT GCG AGC TGG AAA A-3' and reverse primer 5'- GAT GGA GTC GTT GAG GC-3' were used in combination with probe 5'- (FAM)- CCA AAA CCG GAG GAC CAA GT- (TAMRA)-3'<sup>(18,19)</sup>.

## 3. Statistical Analysis

The data collected were statistically analyzed using statistical package for social sciences (SPSS/version 15) software. (Inc., Chicago, USA). Variables considered were

patients, age and gender and disease activity and treatment characteristics. All patients still alive in first continuous remission were censored at their last follow-up. Probabilities of overall survival were calculated using the Kaplan-Meier estimate and P-values were determined using the Log-rank test. The Cox model was used to determine the independent prognostic importance of variables. Further analyses were performed only on patients with available molecular data to evaluate the clinical significance of the genetic mutations. Patient-, disease-, and treatment-related variables of the groups divided according to genetic mutations were compared using the  $\chi^2$  statistic for categorical variables and the Mann-Whitney test for continuous variables. The log-rank test and Cox proportional hazards model were used to determine the univariate and independent prognostic importance of several variables.

## 4. Results

Expression of HOX11L2 and HOX11 were studied in 28 pediatric T-ALL patients. They were 19 patients < 9 years, range from 3-8 years (median 6) and 9 patients > range from 9-13 years (median 10.5). There were 15 male (53.6%) and 13 female (46.4%). The clinical characteristics of these

patients are summarized in table (1). Of 28 patients, 8(28.6%) expressed HOX11L2 and 4(14.3%) expressed HOX11. They were no statistical significance between HOX11L2 and HOX11 expression with respect to age, sex (p= 0.504 and 0.86 respectively), presenting mediastinal mass (P= 0.635, 0.761) and CNS involvements (P = 0.538 and 0.283 respectively). Nevertheless, HOX11L2 and HOX11 strongly correlate with hepatomegaly (P=0.04, 0.001), splenomegaly (P=0.05, 0.022) and lymphadenopathy (P=0.05, 0.001) respectively. White blood cells were significantly higher in HOX11L2 subgroup than HOX 11 (p= 0.014). The clinical responses to treatment of patients with the two oncogenetic subgroup are detailed in table (1). For each subgroup the relationship with outcome was assessed by Kaplan-Meier curves (figure 1 and 2). The overall survival of patients with HOX11L2 expression was lower than of the patients without HOX11L2 expression (log-rank P<0.025). As regards HOX11 expression, a statistically significant difference in clinical outcome was found, where HOX11 expression conferred a prognostic advantage (p< 0.001). We conducted subgroup analyses for all diagnostic parameters, including WBCs, age and sex, response to prednisone. Non of the groups showed a significant difference except poor prednisone response with HOX11 L2 expression (P=0.007).

**Table (1).** Clinical Biological and Molecular ontogenetic analysis of pediatric ALL total number 28.

	HOX11L2			P	HOX11			P
	+ve (8)	-ve (20)			+ve (4)	-ve (24)		
<b>Median age, years at diagnosis:</b>								
< 9 years (no. 19)								
Median	6	4.5	6.5	0.504	4.5	6	0.086	
Range	3-8	3-8	3-7		4-6	3-8		
> 9 years (no. 9)								
Median	11	10.5	11	0.171	6	11	0.102	
Range	9-13	10-11	9-13		3-8	9-13		
Childs gender M/F (15/13):								
M	15(53.6%)	7(87.5%)	11(55%)	0.044	3(20%)	12(80%)	0.628	
F	13(46.4%)	1(12.5%)	9(45%)	0.235	1(7.7%)	12(92.3%)	0.548	
Liver:								
Normal	4(14.29%)	3(37.5%)	1(5%)	0.620	2(50%)	2(9%)	0.896	
Enlarged	24(85.71%)	5(62.5%)	19(95%)	0.049	2(50%)	22(91%)	0.001	
Spleen :								
Normal	3(10.71%)	2(25%)	1(5%)	0.639	2(25%)	1 (4.2%)	0.587	
Enlarged	25(89.29%)	6(75%)/	19(95%)	0.050	2(75%)	23 (95.8%)	0.022	
Lymph nodes:								
Normal	5(17.86%)	4(50%)	1(5%)	0.538	3(75%)	2(9%)	0.239	
Enlarged	23(82.14%)	4(50%)	19(95%)	0.05	1(25%)	22(91%)	0.001	
Mediastinal involvement	11(39.3%)	4(50%)	7 (35%)	0.635	2(50%)	9(37.5%)	0.761	
CNS involvement	5(17.9%)	1(12.5%)	4 (20%)	0.538	2 (50%)	3(12.5%)	0.283	
WBCs median at diagnosis 10 <sup>9</sup> /L	102.5	115	92.5	0.014	67	90	0.059	
Range	6-160	24-152	6-160		6-120	6-160		
Response to pre-phase treatment:								
GPR	12(42.86%)	5(62.5%)	7(35%)	0.469	4(100%)	8(33.3%)	0.167	
PPR	16(57.14%)	3(37.5%)	13(65%)	0.007	0( 0%)	16(66.6%)	0.112	
Failure:								
Early deaths	4(14.29%)	2(25%)	2(10%)	0.099	1(25%)	3(12.5%)	0.365	
Toxic death	6(21.24%)	0( 0%)	6(30%)	0.038	0( 0%)	6(25 %)	0.001	

GPR: good prednisone response; PPR: Poor prednisone response, CNS: Central nervous system, BM: Bone Marrow, PB: Peripheral blood.

Multivariate Cox proportional hazard analyses using WBCs, age, gender and overall survival as variables. Age at diagnosis was given in years, WBCs at diagnosis were given as  $10^9/L$  table (2). A poor response to prednisone and over expression of HOX11L2 independently predicted adverse outcome. The hazard ratio for overall survival patients with poor response to prednisone were 2.3 ( $P=0.001$ ) and 2.7 ( $P=0.01$ ) for patients with HOX11L2 positive T-ALL.

**Table (2).** Multivariate analyses using Cox regression model with factors associated with overall survival.

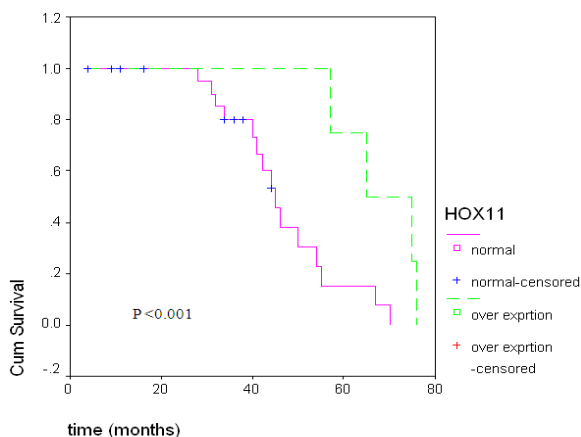
	Hazard ratio	95% CI	P
HOX 11L2	2.698	0.869-1.027	0.012
HOX 11	1.986	0.563-1.658	0.098
WBC	1.00	0.869-1.028	0.325
Age	1.032	0.934-1.327	0.354
Sex	0.758	0.189-1.365	0.741
Response to steroid			
Good 3	0.573	0.475-1.325	0.547
Poor 5	2.325	1.369-6.71	0.001

Univariate analysis COX proportional hazard analysis using overall survival for the HOX11L2 and HOX11. Hazard ratio for each specific oncogenetic subgroup was indicated relative to T-ALL cases lacking that molecular aberration table (3). Only two factors were significantly correlated with lower overall survival rate: a poor response to prednisone ( $P=0.05$ ) and HOX11L2 status ( $P=0.036$ ).

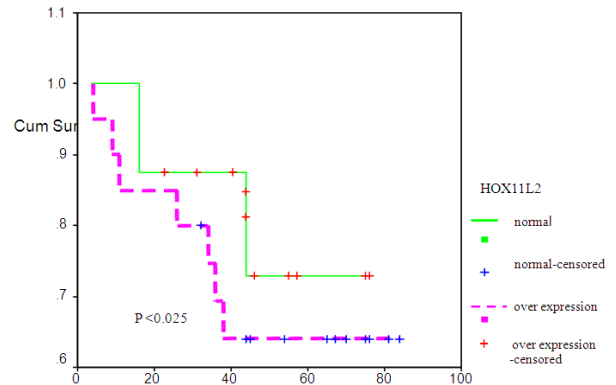
**Table (3).** univariate analyses using Cox regression model with factors associated with overall survival

	Hazard ratio	95% CI	P
HOX 11L2	2.411	0.983-5.681	0.036
HOX 11	0.271	0.698-4.658	0.527
WBC	0.985	0.088-4.058	0.328
Age	0.677	1.396-9.986	0.102
Sex	0.726	0.340-1.625	0.307
Response to steroid			
Good 3	0.963	0.478-2.365	0.05
Poor5	1.211	0.262-6.550	

Overall survival:



**Fig. (1).** Clinical outcome of patients with leukemia cells expressing HOX11 positive and negative cases.



**Fig. (2).** Clinical outcome of patients with leukemia cells expressing HOX11L2 positive and negative cases.

### 5. Discussion

Treatment optimization in acute leukemia requires accurate assignment of patients at diagnosis to specific risk groups to guide subsequent risk adapted treatment stratification. In T-ALL, few prognostic molecular markers have been identified<sup>(17)</sup>. In this study, we had evaluated the impact of expression of the genes HOX11L2 and HOX11 in conjunctions with other clinical factors to predict outcome in T-ALL patients.

A panel of 28 pediatric patients with T-ALL was investigated for the presence of expression of HOX11L2 and HOX11 genes. The expression of HOX11L2 was found in 8 (28.6%) and HOX11 expression was found in 4 (14.3%) patients, in keeping with previous reports by others<sup>(18,19)</sup>. In contrast, *Mauvieux et al*<sup>(20)</sup> was found 60% of cases expressed HOX11L2 and 5% in pediatric cases as regards HOX11 expression by *Bergeron et al*<sup>(21)</sup>.

*Bernard et al*,<sup>(9)</sup> initially reported cases of T-ALL with t(5;14)(q35;q32) and expression of the developmental gene HOX11L2 which belongs to a distinct family of homeobox genes including HOX11, HOX11L1 and HOX11L2. These genes harbor a threonine in the third helix of the homeodomain, which confers specific DNA binding properties<sup>(22,23)</sup>. Ectopic expression of HOX11 in T-ALL is associated with translocations implicating TCR genes t(10;14) and t(7;10) for TCR alpha and TCR beta, respectively<sup>(11,23)</sup>. In T-ALL with t (5;14)(q35;q32), HOX11L2 expression is probably under the influence of the CTIP2 (BCL11B) gene<sup>(9)</sup> located on chromosome 14. The latter gene is strongly expressed in the thymus, and is potentially implicated in T cell differentiation. HOX11L2 activation might occur independent of t(5;14) translocation e.g. microdeletion, submicroscopic inversions lead to transcriptional activation of the gene.

HOX11L2 were significantly express in male than females ( $P= 0.044$ ) and this in agreement with previous studies done by *Fernado 2002*<sup>(24)</sup> suggesting a clear correlation with male sex, that remains unexplained. There were no association was observed with age at diagnosis and this was in agreement with *Mauvieux et al 2002*<sup>(20)</sup>. In

contrast, there was a significant correlation with high white blood cell count ( $P=0.014$ ). As regards HOX11 there was no statistical difference between male and female, age and WBCs.

HOX11L2 and HOX11 were statistically significant with hepatomegaly, splenomegaly and lymphadenopathy. On the other hand, *Ballerini et al 2002*<sup>(18)</sup> failed to find any associations.

In the current study, there was a significant predictor for an association between HOX11L2 and poor outcome. This result was in agreement with some studies<sup>(19,24,25)</sup>, but was on the contrary other studies<sup>(26,21)</sup> indicating that the prognostic relevance of HOX11L2 could be dependent on the therapy given, associations with ABL1 abnormalities, NOTCH1 mutation status and CD1 positivity<sup>(20,27)</sup>. The high frequency of HOX11L2 deregulation in T-ALL suggests its involvement as a key pathway for leukomogenesis.

The present study showed that patients with leukemia cells expressing HOX11 tended to have better clinical outcome compared to the other patients in the study. This is in accordance with previous studies<sup>(19,28)</sup>.

The difference in the prognosis between HOX11L2 and HOX11 may be due to these subgroups are arrested at slightly different T-cell developmental stages and therefore may have different responses to therapy. The presence of different immunophenotypic markers between HOX11L2 and HOX11 supports this view. HOX 11 rearranged T-ALL is arrested at a strictly early cortical<sup>(29,30)</sup> or immature-B developmental stage while HOX11L2 – rearranged T-ALL comprises both immature and TCR alpha delta-positive mature cases<sup>(31)</sup>.

In conclusion, the present study showed that the outcome of HOX11L2 and HOX11 expression differs, with poor outcome for patients with HOX11 L2 expression.

Cytogenetic, molecular and immunologic studies should be combined in larger series, in order to confirm the correlation between cytogenetic abnormalities, phenotype and HOX11L2 and HOX11 gene expression and to specify its prognostic significance<sup>(32)</sup>. Future molecular diagnostics may make use of such leukemia-specific markers as HOX11L2 and HOX11 to detect minimal residual disease.

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