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Review Article

Fusion of ZNF384 with Different Genes at Acute Lymphoblastic Leukemia Patients

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Abstract

Zinc finger protein 384 (ZNF384) fusion is good indicator in diagnosis; furthermore, ZNF384-rearregment is prevalent in mixed-phenotype acute leukemias. Last time is reported fusion of ZNF384 with 7 other partners in ALL. It is reviews in details the type the types of chromosomal aberrations, their background correlation with immunophenotype and distribution and their prognostic relevance.

Keywords: Acute Lymphoblastic Leukemia; B-Cell; ZNF384; Gene Fusion; Ewing Sarcomas

Introduction

Acute lymphoblastic leukemia (ALL) is a heterogenous disease at the demographic, clinical and genetic levels. ALL can occur at any age, but is more prevalent among children (age 3 - 6 years old). It is shown that in England more than 50% of patients are between 0-14 years old, and just 20% are 60 years old. The ratio between male and female which are diagnosed with ALL are 1.4:1, so male are little more frequently than female. Survival rates from ALL have improved dramatically over the past four decades but vary significantly with age. Children which are treated with modern protocols have survival rates exceeding 90% [1,2].

Survival from adult ALL is approximately 40% for those patients aged between 25 and 59 years old and is significantly lower 20% for older adults [3,4].

It is shown that ALL is characterized by the sequential acquisition of genetic aberrations which drive the initiation and maintenance of the leukemic clone [5].

Fusion of genes in ALL

B – Cell precursors is heterogeneous diseases that can be subdivided according genetic abnormalities. Till today are reported for many gene infusion in ALL. Last time is reported that ZNF384 is fused in B cell precursor ALL and seven fusion partners.

ZNF384 gene encodes a transcription factor that regulates promoters of extracellular matrix gene and also is involved in ALL through fusion with the TET family genes, {Ewing sarcoma breakpoint region 1 gene -EWSR1, t (12; 22), TATA box binding protein-associated factor-TAF15, t (12;17), transcription factor 3-TCF3, t(12;19) [6-8].

Hirabayashi., *et al*. identified a total of 15patients with TCF-ZNF384, 3 patients with TAF15-ZNF384 and 3 patients with CREBBP-ZNF384, respectively [9].

It is shown that in 3 out 15 TCF3-ZNF384 patients the fusion point is at exon 11 of TCF3 and exon 3 of ZNF384 [8].

Than it is shown fusion of exon 13 of TFC3 and exon 3 of ZNF384 in seven patients, in three patients it is shown fusion of exon 6 of TAF15 and exon 3 of ZNF384; in CREBBP-ZNF384, Hirabayashi S., *et al*. [9] identified fusion of exons 4, 5, 6 of CREBBP with exon 3 or 2 of ZNF 384, in contrast exon 7 of CREBBP was fused out of frame to exon 3 of ZNF384 in one patients.

In the case of fusion of NMP2K-ZNF384 it is found fusion of exon 15 and exon 14 with exon 3 of ZNF384 [9].

Gene fusion involving ETV6 is detected in B cell ALL patients. The most common gene fusion observed has been RTV6-RUNX1 fusion, which results from the t (12;21) (p13; q22). It is shown that KMT2A gene also is fused in ALL. Of ten fusion KMT2A gene cases half are observed in ALL, and the other half was observed in AML.

The gene fusion of PBX1-TCF3 is detected by SNP array. Most frequently gene fusion which is detected is t (1:19) (q23; p13.3). This fusion is unbalanced translocation and is results of derivate of chromosome 19 including duplication of chromosome 1, and loss of small region in 19q13.3 gene fusion ZNF 384-TCF3 generated by unbalanced t (12:19) (p13; p13) is detected by SNP array in a single cases.

EBF1 gene fusion is involved in six B-ALL patients. The fusion is shown between genes EBF1-PDGFRB (5q32q33.3) resulting in copy number of two for this regions.

The gene fusion of STIL-TAL1 it is shown in five ALL cases and one T cell lymphomas.

Another gene fusion detected in ALL is fusion of gene LMO2-RAG1, when is detected proximal deletion of 11p12p13 and distal breakpoint located within the RAG1 gene [10].

In pediatric patients it shown gene fusion of ZNF384 and MEF2D (myocyte enhancer factor 2D) in 3%-4% of children and approximately 6%-7% of adult patients, respectively [11-14].

Gu., *et al*. report that MEF2D ALL is associated with older age onset, an aberrant immunophenotype (CD10 negative, CD38 positive), and poor outcome [11].

Iacobucci., *et al*. show that ZNF384 involve the fusion of a 5' partner gene, usually a transcriptional regulator or chromatin modifier (EP300, CREBBP, TAF15, SYNRG, EWSR1, TCF3, and ARID1B), to the entire coding region of ZNF384 [15].

ZNF384 rearranged ALLs are often diagnosed as B-ALL with expression of myeloid antigens or as B/myeloid mixed-phenotype acute leukemias. ZNF384 has intermediated prognosis in B-ALL and also is characterized by upregulation of the JAK-STAT pathway [13].

Alexander., *et al*. 2018 say that rearrangement of ZNF384 are present in 48% of cases of B/M MPAL, involving TCF3 (n = 8), EP300 (n = 5), TAF15 (n = 1) and CREBBP (n = 1) [16].

The genomic landscape of childhood ZNF384r B –ALL (n = 19) was similar to that of ZNF384r MPAL with the exception of KDM6A alternations [16].

Analysis of different range of acute leukaemias, showed that the gene expression profiles (GEPs) of ZNF384 B/M MPAL and B-ALL were indistinguishable. Patients with ZNF384 exhibited higher FLT3 expression those with other types of B/M or T/M MPAL.

Gene set analysis suggested that ZNF384 B/M MPAL was arrested at a more mature stage of development than other types of B/M MPAL.

However, compared with B-ALL, the ZNF384 leukaemia showed enrichment of stem cell pathways and genes upregulated in ETP-ALL.

Alterations identified in the unfractionated samples (for example, TCF3–ZNF384 and mutations in MYCN, NTSD2 and DNAH17 in the ZNF384 r sample) were identified in the purified blast populations but not in non-leukaemic T or natural killer (NK) cells [16].

The TCF3-ZNF384 fusion it is shown by a reciprocal translocation between chromosomes 12 (ZNF384 in 12p13) and 19 (TCF3 in 19p13) [17].

Two classes of in frame fusions –one with MEF2D as the N-terminus partner and the other with ZNF384 as the C-terminus partner-were noteworthy for their frequent occurrence in our cohort

and the disruption of partner genes involved in transcriptional regulation.

From the combined data, the MEF2D fusions were found in 12 of 177 (6.8) adult and 7 of 199 (3.5%) pediatric patients, with ZNF384 fusions identified in 13 of 177 (7.3%) adult and 8 of 199 (4.0%) pediatric patients.

Liu., *et al*. 2016 report that from leukemic cells from patients with ZNF384 fusions were more CD10-negative than were those from other patients in both the adult (15.8% vs. 5.3%, P = 0.04) and pediatric (18.8% vs. 2.9%, P = 0.02) cohorts; and to co-express myeloid –associated antigen CD13 and/or CD33 (13.1% vs. 0, P = 0.001 in adults; 12.1% vs 1.7%, P = 0.02 in children). Liu., *et al*. 2016 shown that no significant survival differences between patients with or without ZNF384 fusions in either the adult (38.6% vs29.6% or pediatric cohort (75% vs 69.4%) [12].

Qian., *et al*. report that in patients with EP300-ZNF384 fusion did not express a Ph-like gene signature. Eight of nine patients had identical break points at EP300 exon 6 (22q13) and ZNF384 exon 3 (12p13), with the remaining patient having a ZNF384 breakpoint in exon 2 [18].

In contrast to other reports where ZNF384 fusions have multiple 5′ partners, both Yasuda., *et al*. 2016 and Gocho., *et al*. 2015 has detected EP300-ZNF384 fusions in 5.7% of BCR-ABL1-negative AYA/adult pre-B-ALL, making it one of the more prevalent recurrent lesions in this age group. The EP300ZNF384 patients cluster in the AYA range have reduced CD10 surface expression and up-regulated CD33 expression in common with previous reports [13,19].

The EP300-ZNF384 subgroup showed improved outcome compared to other pre-B-ALL patients studied, and concurs with a Japanese cohort where ZNF384 fusions have better survival outcomes than Ph-like ALL in AYA [13,20].

Haslinger S., *et al*. report that in twelve Austrian patients it is shown of ZNF384 fusion in eight patients with EP300 and in two with TCF3. Two others had novel fusion partners, one of which was ascertained as CCAR1 [21,22].

Yasuda T., *et al*. found that DUX4, ZNF384 and MEF2D fusion genes account for -40% of Ph- B cell AYA-All cases, with chromosomal rearrangements thus being a characteristics feature of this disorder that distinguishes it from B cell ALL at other ages [13].

Conclusion

ALL is complex diseases with heterogeneous clinical, and cytogenetic characteristics. In this review is shown cytogenetic change and variety of chromosomal aberrations. Given that, multicenter collaboration will be required to determine the whole spectrum of genetic abnormalities and their prognostic importance and define whether adult and pediatric ALL have different behavior. The cytogenetic analysis should perform in all ALL patients. The genetic studies with novel genomic technologies should help to define the genetic basis and the leukemogenic mechanisms of this diseases and stratify patients to different therapies based on cytogenetic and molecular analysis.

Conflict of Interest

No conflict of interested declare.

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