Introduction

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are highly aggressive malignant tumors that originate from precursor T-cells, B-cells or lymphoblasts (1-3). LBL is the second most common subtype of non-Hodgkin’s lymphoma (NHL) in children and adolescents, accounting for approximately 2% of all NHL cases (4). T-cell LBL (T-LBL) accounts for nearly 90% of all LBL cases and tends to occur in children and adolescents, predominantly in males (3). In contrast with T-LBL, T-ALL is not as common as B-cell ALL (B-ALL) and accounts for nearly 15% of all childhood ALL cases. T-ALL and T-LBL have similar morphological, immunophenotypic, and clinical features; therefore, the World Health Organization (WHO) classification has unified these entities as precursor T-cell lymphoblastic leukemia/lymphoma (pre-T-ALL/LBL). In this review, we use the term T-ALL/LBL to refer to both T-ALL and T-LBL.

With the current intensive combinations of chemotherapy with or without local radiotherapy, a 5-year EFS of approximately 60–90% can be achieved (5-7). Despite these acceptable EFS rates, the 5-year overall survival (OS) rate of relapsed patients remains poor—only approximately 3–12% (8-11). Therefore, precise and effective prognostic parameters are highly needed.
to predict the prognosis of T-LBL, the validity of these parameters is insufficient, unreliable and nonspecific. Understanding the significance of gene mutations in the prognosis of disease can help to stratify the risk of disease, identify individualized treatment for patients with different risks, and improve the prognosis of patients. For example, preventing relapse is important in patients identified to have a high risk of relapse; in contrast, for low-risk patients, significant acute and long-term toxicity caused by current treatment regimens should be avoided if the treatment intensity can be reduced without affecting the outcome. Future studies focusing on these aspects and novel prognostic indicators will undoubtedly contribute to this understanding. Risk groups are stratified and given appropriate treatment options accordingly, bringing unanticipated results. Gene expression profiling has identified several potential prognostic indicators of inherited T-LBL, such as NOTCH1, F-box and WD repeat domain-containing 7 (FBXW7), phosphatase and tensin homolog (PTEN), loss of heterozygosity at chromosome 6q (LOH6q), CASP8-associated protein 2 (CASP8AP2), c-MYC, interleukin-7 (IL-7), CALM-AF10, and cyclin-dependent kinase inhibitor 2A/B (CDKN2A/B). Although most of these are controversial, they help to distinguish disease severity in patients, guide therapy in the clinic, and predict prognosis.

NOTCH1

Over 50% of T-LBL patients carry activating mutations of the gene NOTCH1 (12,13), and the frequency of NOTCH1 activating mutations between pediatric and adult patients with T-LBL is not significantly different (14). Activating mutations of NOTCH1 mainly result from the t(7;9) (q34;q34.3) translocation, the most common genetic abnormality found in T-LBL (15).

NOTCH1 is a transmembrane receptor that can bind to ligands and lead to a series of protein cleavages. After the notch intracellular domain (NICD) is released, it binds to the transcribed regions of genes such as c-MYC, HES1, and NF-κB and plays its role. Mutation of NOTCH1 mainly affects two domains, the extracellular heterodimerization domain (HD) and proline-glutamic acid-serine-threonine (PEST) domain, which can lead to non-ligand-dependent activation of transmembrane receptors and abnormal activation of downstream genes (15-18). The Notch signaling pathway plays a key role in regulating development and differentiation via diverse cellular processes, such as differentiation, proliferation, apoptosis, adhesion, cell cycle progression, spatial development, and stem cell maintenance and self-renewal, as well as in the normal development of many tissues and organs. In addition, NOTCH1 is necessary and sufficient for the development of T-cells (19,20). Accumulating evidence supports NOTCH1 as a tumor suppressor. NOTCH1 plays a role in suppressing cancer mainly by promoting cell cycle exit and cell differentiation, thereby reducing the potential of cancer stem cells and tumor-initiating cells (21).

Numerous studies indicate a good prognosis and an improved treatment response in T-ALL/LBL patients, especially children, with NOTCH1 activating mutations (22-24), even though these mutations can reverse the effects of other adverse prognostic factors, such as PTEN and RAS mutations (13). Another study indicated more favorable survival for NOTCH1 mutation-positive patients than for NOTCH1 mutation-negative patients (15). Bandapalli et al. previously analyzed the effects of PTEN and NOTCH1 mutations on prognosis in 301 ALL-BFM treated children with T-ALL and found that NOTCH1 mutation was the most important favorable prognostic factor. Regardless of the PTEN mutation status, T-ALL patients with NOTCH1 mutation showed favorable induction sensitivity and prognosis (25). The absence of NOTCH1 mutation and the presence of other adverse prognostic factors may lead to poor outcome, and children have a better prognosis than adult patients (15).

γ-secretase inhibitors (GSIs) can block the proteolytic cleavage of NOTCH1 receptors as well as suppress the release of activated NOTCH1 (the NICD) from the membrane, and have been proposed as a potential therapeutic strategy in T-ALL (15,26). However, GSIs are clinically effective only for a small proportion of patients with NOTCH1 activating mutations. Other concurrent factors, such as the PI3K-AKT-mTOR signaling pathway and cycling protein kinase D downstream of NOTCH, may influence the effectiveness (13). Moreover, the study of activating mutations of NOTCH1 provides a strong basis for targeted therapies interfering with the NOTCH signaling pathway (12). However, due to our poor knowledge of T-ALL pathogenesis, further investigation is needed, and novel approaches for diagnosis as well as treatment are urgently needed.

FBXW7

FBXW7, a component of the Notch signaling pathway, is
also involved in cell proliferation, apoptosis, the cell cycle and differentiation. FBXW7 is a member of the F-box protein family and a component of the E3 ubiquitin ligase complex that recognizes the PEST domain in the NICD and accelerates the termination of NOTCH1 signaling in the nucleus (27). FBXW7 encodes a protease that degrades the NICD in the NOTCH1 signaling pathway. Mutation of FBXW7 can lead to the loss of recognition of NOTCH1 and reduce NICD degradation, subsequently leading to abnormal activation of the NOTCH1 pathway (13,18). Dysregulation of NOTCH1 signaling can lead to hyperactivation and confer a proliferative advantage on tumor cells in several cancers, ultimately resulting in developmental defects. In addition, FBXW7 is strongly correlated with NOTCH1 mutations, and they commonly occur concurrently (13,28).

Although the mutation frequency of FBXW7 is less than 15% in T-ALL patients (16), FBXW7 has been considered a candidate prognostic marker in association with NOTCH1 mutation (18,29). Numerous studies have been conducted and found that the prognosis of T-ALL patients with FBXW7 mutation is more favorable than that of patients without FBXW7 mutation (13,29,30). However, in one meta-analysis, FBXW7 mutation did not significantly affect the prognosis of children or adults with T-ALL (15).

Regarding the concurrent mutation of FBXW7 and NOTCH1, more than 83% of T-ALL patients with FBXW7 mutation also harbor NOTCH1 mutation (30). T-ALL patients with concurrent NOTCH1/FBXW7 mutation had better prognoses (22,31-33) and a 5-year relapse-free survival (RFS) rate of greater than 85%. NOTCH1/FBXW7 mutation also had the same favorable prognostic effect in children with T-ALL (13). A study analyzing NOTCH1 and FBXW7 mutations in 50 South Indian T-ALL patients treated with a regimen modified from the ALL/NHL-Berlin-Frankfurt-Münster (BFM) 95 trial showed that T-ALL patients with NOTCH1/FBXW7 mutation had better RFS than patients without NOTCH1/FBXW7 mutation in Kaplan-Meier survival analysis of 50 patients with T-ALL (18). However, a few studies have reported no significant difference (34-36) or poor prognosis in NOTCH1/FBXW7-mutated patients compared with that in patients without NOTCH1/FBXW7 mutation (37,38). Perhaps the outcome is also influenced by the treatment protocol used at the same time or at other times. Therefore, the significance of the double mutation of NOTCH1/FBXW7 remains to be further studied.

PTEN

The tumor suppressor PTEN, located on chromosome band 10q23, can negatively regulate phosphatidylinositol 3-kinase (PI3K)-AKT signaling, which plays a key role in cellular metabolism, proliferation and survival (39,40). Expressed PTEN has a dephosphorylation function; it can remove the phosphoric acid moiety from phosphatidylinositol 3,4,5-trisphosphate (PIP3) to form phosphatidylinositol 4,5-bisphosphate (PIP2), resulting in PI3K-AKT signaling pathway blockade (41). Inactivation of PTEN may lead to overactivation of the PI3K-AKT signaling pathway, uncontrolled cell proliferation, and even to malignant tumors (42). Deletion or mutation of PTEN in T-LBL/ALL was initially found in cell lines (43,44), and restoring PTEN expression can suppress the PI3K-AKT signaling pathway, which in turn promotes apoptosis (45).

PTEN deletion or mutation is one of the most common oncogenic mutations in T-ALL/LBL. Deletion or mutation of PTEN is reported to be found in over 20% of patients with T-ALL, and deletion or mutation of PTEN usually does not occur along with NOTCH1 and FBXW7 mutations (13). Clinical observation showed that the disease-free survival (DFS) rate of patients with PTEN mutation in T-LBL (0.59±0.12) was significantly lower than that of T-LBL patients with wild-type PTEN (0.82±0.04, P=0.014) (46). T-LBL patients with PTEN mutation seem more insensitive to hormone therapy and exhibit a poorer response than T-LBL patients with wild-type PTEN (25). Some studies have found that deletion or mutation of PTEN is associated with poor prognosis and that NOTCH1 mutations can overcome the negative effects of PTEN mutation (25,46), but the mechanisms remain unclear. However, deletion or mutation of PTEN cannot reverse the favorable prognostic effect of NOTCH1/FBXW7 mutation, with only a nonsignificant decrease in OS (13,47). Some centers have identified PTEN as a significant, independent risk factor for relapse in T-ALL patients treated with various protocols (25,48-50). Moreover, T-ALL patients with RAS and/or PTEN mutations showed notably unfavorable survival compared to that of T-ALL patients without mutations in the French Group for Adult T-ALL Research (51).

PTEN deletion has been proposed to be associated with GSI resistance in T-ALL patients in a manner dependent on NOTCH1 (48,52,53), but some issues remain to be investigated further (42). However, this finding provides a
new clinical therapeutic target.

**LOH6q**

LOH6q is not uncommon in various hematological malignancies, especially T-ALL/LBL (54,55). LOH6q is reported to be the first molecular parameter described to be related to the prognosis of pediatric patients with T-LBL (56).

Burkhardt et al. analyzed the 108 T-LBL patients and 127 T-ALL-patients, and reported that the frequency of LOH6q is detectable at similar frequencies about 20% in both T-ALL and T-LBL (54,57). However, the commonly deleted regions are different in terms of the prognostic relevance of LOH6q (54). Numerous studies found that LOH6q is associated with an increased risk of relapse in T-LBL patients but not in T-ALL patients, although both are considered to be different presentations of different stages of the same disease (54,57-59). Another study from Burkhardt et al. confirmed that LOH6q was highly significantly correlated with poor outcome and increased risk of relapse in a retrospective analysis of T-LBL patients treated with NHL-BFM protocols (55).

In addition, the clinical features of LOH6q T-ALL/LBL patients were not significantly different from those of LOH6q patients, except for a trend towards younger age in LOH6q patients than in LOH6q patients (54,58). In addition, some centers claimed that NOTCH1 mutations were observed only in patients with LOH6q mutations (58). Further knowledge of the genetic landscape of pediatric T-ALL/LBL is hampered by the rarity of patient material for molecular biological research. Therefore, sufficient availability of material is needed for future studies.

**CASP8AP2 (FLASH) deletion**

The CASP8AP2 protein is encoded by the CASP8AP2 gene, located at chromosome region 6q15 in humans (60). CASP8AP2, also known as FLICE or FLASH, was initially identified as a proapoptotic protein transmitting apoptosis signals via involvement in the glucocorticoid signaling pathway (22,61). More recently, various functions have been found, including TNF-induced activation of NF-kappa B, mediation of S-phase cell cycle progression and cell proliferation, and regulation of the transcription and maturation of the 3’ end of histone mRNAs (60,62,63). It is possible that more functions remain to be investigated.

The clinical significance of CASP8AP2 in childhood ALL was first reported by Flotho et al., who associated the expression of different genes with the in vitro response to chemotherapy in ALL patients, demonstrating that decreased expression of CASP8AP2 was associated with dramatically increased rates of minimal residual disease (MRD) and hematological relapse (60,64,65). In addition, this result was verified in another study showing that CASP8AP2 expression in patients with newly diagnosed ALL is a valuable marker for predicting relapse (66). CASP8AP2 deletion is particularly frequent (50%) and adult ALL patients with CASP8AP2 deletion had a lower 18 months event-free survival (EFS) (31% vs. 41%) and a higher relapse rate (70% vs. 37%, P=0.02) compared with patients without CASP8AP2 deletion. Furthermore, other possibilities for CASP8AP2 silencing should also be considered (60,67).

Although both miR-210 and CASP8AP2 expression act as prognostic indicators in pediatric ALL, and CASP8AP2 is a target of miR-210 in bone marrow stem cells, there is no evidence revealing any association between CASP8AP2 and miR-210 expression in ALL patients (66). In addition, one study showed that the combined expression of these molecules predicted relapse in ALL patients. Among patients with high expression of both genes, none relapsed, while the group of ALL patients with low expression of both genes exhibited the poorest outcomes for 3-year RFS, EFS and OS, and no statistically significant difference was observed in any of the 3 prognostic indexes for low expression of either gene alone (66). Therefore, combining the expression of miR-210 and CASP8AP2 may more precisely predict whether patients are at increased risk of relapse.

The expression of CASP8AP2 can also be influenced by E2F3a. E2F3a can enhance the transcriptional activity of CASP8AP2 directly. Moreover, overexpression of E2F3a promotes the sensitivity of leukemic cells to chemotherapeutic drugs by increasing the proportion of leukemic cells in S and G2/M phases and accelerating proliferation (61,64). Additionally, downregulation of CASP8AP2 reverses the promotive effect of E2F3a on chemotherapeutic sensitivity (61). Thus, in childhood ALL, the prognostic significance of CASP8AP2 expression may be actualized by E2F3a.

While the biological basis of the variation in CASP8AP2 expression should be considered, the occurrence of a deletion at the chromosome 6q15-16.1 region (22), corresponding to the gene’s location, in some patients with T-ALL could lead to downregulation of CASP8AP2 and
poor response to early treatment (61). In addition, this deletion can lead to a decrease in CASP8AP2 expression, and these effects may be associated with the presence of MRD (60). In addition, combining CASP8AP2 expression with the presence of MRD can contribute to distinguishing patients with an increased risk of bone marrow relapse.

A previous study reported that low expression of CASP8AP2 was related to high rates of MRD and relapse (61,68). However, the mechanisms of CASP8AP2 downregulation in childhood ALL remain unclear.

c-MYC

The c-MYC gene is a protooncogene coding for a transcription factor that plays a major role in many processes, including the cell cycle, apoptosis and cellular transformation (69). Mutation of c-MYC may lead to dysregulated expression of many genes involved in cell proliferation and may even ultimately result in the formation of cancer. The correlation of BCL-2 and c-MYC translocation with poor prognosis in B-cell lymphomas was first indicated by Kanungo et al. (70), and the correlation of BCL-2 and c-MYC gene rearrangement was later found in adults with lymphoblastic leukemia/lymphoma (71). In addition, BCL-2 and c-MYC may play a vital cooperative role in the pathogenesis of ALL/LBL (69).

Recently, expression of c-MYC has been found to play an important role in the occurrence and development of T-LBL/ALL and is strongly associated with poor prognosis. In addition, c-MYC expression can be an independent prognostic factor for T-LBL/ALL (72). This result was also observed in a later study. The study further presented the association between the expression of c-MYC and the prognosis of patients via analysis of 90 patients with T-LBL/ALL (the positive group) and 30 patients with lymph node reactive hyperplasia (the control group). The rate of positive c-MYC protein expression was positively correlated with Ki-67 expression and was significantly higher in the positive group than in the control group, while the inverse correlation was seen between positive c-MYC protein expression and OS, suggesting that patients with c-MYC protein expression may have worse prognoses (73). Thus, c-MYC can be used as a parameter to predict the clinical outcome of patients with T-ALL/LBL.

IL-7R

The interleukin-7 receptor (IL-7R) is a cell surface protein that plays a critical role in the development of T-cells and is important for the immune system (74-77). Loss-of-function mutations in this receptor can lead to severe combined immunodeficiency (SCID), which is an intractable disease (75,77,78).

Approximately 10% of patients with T-ALL have activating mutations of IL-7R (79). Recently, studies showed that IL-7 and IL-7R may contribute to T-cell leukemia progression and that 9% of patients with T-ALL display somatic gain-of-function IL-7R exon 6 mutations (74,77). Additionally, considerable evidence indicates that IL-7 and IL-7R are involved in T-cell leukemogenesis in humans (77,80). The involvement of mutational activation of IL-7R in human T-cell leukemogenesis lays the foundation for therapeutic targeting in T-ALL mediated by IL-7R (77). However, some obstacles remain to be addressed. Steroids are the basis of current chemotherapy regimens for the treatment of T-ALL/LBL. However, recent studies have found that steroid resistance is not uncommon in patients with ALL, is associated with poor prognosis and increases the risk of recurrence (81,82). Steroid resistance is mainly caused by activation of the main IL7R signaling pathway components, MEK-ERK and AKT, which are located downstream of the IL7R signaling pathway. This activation induces a strong antiapoptotic response mainly by upregulating the expression of BCL-XL. In addition, IL-7R inhibitors can enhance the effect of steroids (83,84), but other related toxicities may remain to be further explored. Moreover, the IL-7R gene expression levels in blood may reflect the rate of aging and the health status of elderly individuals (85).

CALM-AF10

CALM-AF10, also known as PICALM-MLLT10, is a classical oncogene marker in various malignant tumors (86) and is considered to be the most common fusion protein resulting from the t(10;11) (p12;q14) translocation (86), which is found in immature acute myeloid leukemia (AML), ALL and malignant lymphoma (87,88). CALM-AF10 was originally found in a patient with diffuse histiocytic lymphoma and later became the most common fusion protein in T-ALL (89,90). CRM1 was found to recruit CALM-AF10 into the HOXA cluster, resulting in increased expression of the HOXA gene and eventual cell transformation. Thus, CALM-AF10 causes the occurrence of leukemia mainly by upregulating the expression of Hox homeobox genes, including HOXA5, HOXA7, HOXA9 and
The incidence of CALM-AF10 in patients with T-ALL, including both adults and children, is reported to be greater than 10% (93). Patients with CALM-AF10+ acute leukemia were previously found to typically have poor prognoses (86,90,93), but this finding was mainly based on sporadic reports and had not been evaluated in prospective clinical trials of ALL or AML (86,94,95). Indeed, subsequent studies found no difference in the 3-year EFS and OS between the CALM-AF10+ and CALM-AF10− groups (93).

Based on the pathogenic mechanism of leukemia induced by CALM-AF10 (92), it is proposed that nuclear export inhibitors be included in the treatment of CALM-AF10+ leukemia (89,92). However, no relevant studies have been conducted, and the potential side effects need further exploration. In addition, CALM-AF10+ leukemia cells are more sensitive to iron-restricted growth inhibition than normal hematopoietic cells, and the tumor burden in the spleen appears to be reduced by dietary iron restriction (96,97). However, whether the iron depletion strategy improves the prognosis of CALM-AF10+ leukemia patients has not been verified. Considering the side effects, this treatment modality remains to be investigated further.

Analysis of chromosomal translocations contributes to the understanding of the biological characteristics of various hematological malignancies (98) and provides novel ideas for advanced methods of disease diagnosis and classification and even new targets for the treatment of hematological malignancies (90).

CDKN2A/B

The CDKN2A/B genes, located at chromosome region 9p21, are tumor suppressor genes frequently involved in various human cancers, such as pediatric ALL, breast cancer, lung cancer, and pancreatic cancer (99-102). The CDKN2B gene encodes the cyclin-dependent kinase inhibitors p16INK4A and p15INK4B, while CDKN2A encodes the alternative reading frame protein p14ARF (103). These 3 proteins, as components of the RB1 and TP53 pathways, negatively regulate the G1-S transition in the cell cycle during proliferation to maintain normal cell growth (99). Therefore, inactivation of CDKN2A/B may lead to growth that is rapid or out of control and even to the subsequent formation of cancer. Deletion is one form of inactivation.

Over 60% of childhood T-ALL cases are found to exhibit deletions of the CDKN2A/2B genes at first presentation (99,104). Most CDKN2A/B deletions can be detected at initial diagnosis or at relapse, suggesting that CDKN2A/B deletions are a marker of poor prognosis (99,105). Studies have found that deletion of the CDKN2A/B genes is associated with poor survival outcomes in pediatric ALL (106,107) and that the OS rate of children with ALL is significantly lower in India than in other countries (108). In addition, some studies have found that CDKN2A/B deletions are associated with poor outcomes in B-ALL patients (102,109).

CDKN2A/B can be used as a target for the treatment of T-ALL. Currently, cyclin-dependent kinase inhibitors are being tested in clinical trials for various cancers and have been clinically used to treat breast cancer (110). Moreover, whether this treatment approach can be extended to other cancers, such as childhood ALL or colorectal cancer, is being investigated further (111). Future studies should highlight the combined use of CDK4/6 inhibitors with other targeted drugs, which still face enormous challenges, such as clinical efficacy and cytotoxicity (99).

Conclusions

Although current treatment protocols have improved the overall outcome for patients with T-ALL/LBL, challenges remain, including further improvement in survival rates accompanied by reductions in acute and long-term toxicities and decreasing rates of secondary malignancies. A significant number of patients remain at high risk of relapse, and few individuals survive recurrence. Currently, no useful prognostic parameters have been confirmed for appropriate treatment stratification of T-ALL/LBL. Hence, knowledge of molecular genetic abnormalities can help us not only understand the pathogenesis of disease but also establish more complete risk stratification approaches to identify patients with high-risk factors and develop appropriate individualized treatment to reduce recurrence and improve treatment efficacy. Balbach et al. analyzed of outcome in pediatric T-LBL and proposed a new genetic classifier defining three risk groups: (I) good-risk group, defined by NOTCH1 mutation and no RAS or PIK3-AKT pathway mutation. (II) Intermediate-risk group including all non-GR and non-high-risk patients. (III) High-risk group, defined by NOTCH1 wild type in combination with PTENmut- and LOH6q-positive patients (46). They proposed that for the high-risk group, analogous to treatment of pediatric high-risk T-ALL patients, new drugs and allogeneic stem cell transplantation in first remission should be considered. In contrast, for the low-risk group, treatment de-escalation may be a future option (45). We cannot use this classifier for all the type of T-ALL/LBL patients, because through our review, we learned about the mutated genes between LBL
and ALL, the mutations between adult and children have great differences in the frequency of mutations, mutation sites, and prognosis. The reasons for the inability to analyze are different mutation rates, low incidence, different implementations, and other important factors without detailed stratification.

One of the most important aspects of evaluating patients’ prognosis is simply assessing MRD. Combining cancer-associated genes with the MRD status may improve the accuracy of predicting the prognosis of patients and the risk of recurrence and may provide more effective guidance for later clinical use. In addition, gene mutations can be used as therapeutic targets—for example, Notch pathway inhibitors such as γ-secretase antagonists, NF-kB pathway inhibitors such as bortezomib, or epigenetic drugs such as decitabine.

This review highlights several gene mutations with a high frequency or a strong influence in T-ALL/LBL and indicates that the actual incidence of T-ALL/LBL mutations is much higher than currently recognized. The development of multicenter clinical trials and molecular genetics research aimed at understanding the biology of these diseases offers promise for targeted and more effective therapy in the future.

Acknowledgments

Funding: This work was supported by a grant from the National Natural Science Foundation of China (Henan Joint Fund, Grant No. U1404308) and National Natural Science Foundation of China (Young Scientists Fund, Grant No. 31500833).

Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2019.10.04). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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References

1. Potter MN, Cross NC, van Dongen JJ, et al. Molecular evidence of minimal residual disease after treatment for leukaemia and lymphoma: an updated meeting report and review. Leukemia 1993;7:1302-14.
2. Portell CA, Sweetenham JW. Adult lymphoblastic lymphoma. Cancer J 2012;18:432-8.
3. Lepretre S, Graux C, Touzart A, et al. Adult T-type lymphoblastic lymphoma: Treatment advances and prognostic indicators. Exp Hematol 2017;51:7-16.
4. A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin’s Lymphoma. The Non-Hodgkin’s Lymphoma Classification Project. Blood 1997;89:3909-18.
5. Pillon M, Piglione M, Garaventa A, et al. Long-term results of AIEOP LNH-92 protocol for the treatment of pediatric lymphoblastic lymphoma: a report of the Italian Association of Pediatric Hematology and Oncology. Pediatr Blood Cancer 2009;53:953-9.
6. Sandlund JT, Pui CH, Zhou Y, et al. Effective treatment of advanced-stage childhood lymphoblastic lymphoma without prophylactic cranial irradiation: results of St Jude NHL13 study. Leukemia 2009;23:1127-30.
7. Wang Y, Chen B, Wang Z, et al. Marsdenia tenacissimae extraction (MTE) inhibits the proliferation and induces the apoptosis of human acute T cell leukemia cells through inactivating PI3K/AKT/mTOR signaling pathway via PTEN enhancement. Oncotarget 2016;7:82851-63.
8. Goldberg JM, Silverman LB, Levy DE, et al. Childhood T-cell acute lymphoblastic leukemia: the Dana-Farber Cancer Institute acute lymphoblastic leukemia consortium experience. J Clin Oncol 2003;21:3616-22.
9. Oudot C, Auclerc MF, Levy V, et al. Prognostic factors for leukemic induction failure in children with acute lymphoblastic leukemia and outcome after salvage therapy: the FRALLE 93 study. J Clin Oncol 2008;26:1496-503.
10. Burkhardt B, Reiter A, Landmann E, et al. Poor outcome for children and adolescents with progressive disease or relapse of lymphoblastic lymphoma: a report from the berlin-frankfurt-muenster group. J Clin Oncol 2009;27:3363-9.
11. Pishko A, Nasta SD. The role of novel immunotherapies in non-Hodgkin lymphoma. Transl Cancer Res 2017;6:93-103.

12. Weng AP, Ferrando AA, Lee W, et al. Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia. Science 2004;306:269-71.

13. Guan W, Jing Y, Yu L. Prognostic Value of Recurrent Molecular Genetics and Epigenetics Abnormity in T Lymphoblastic Lymphoma/Leukemia-Review. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2017;25:587-91.

14. Huh HJ, Lee SH, Yoo KH, et al. Gene mutation profiles and prognostic implications in Korean patients with T-lymphoblastic leukemia. Ann Hematol 2013;92:635-44.

15. Liu RB, Guo JG, Liu TZ, et al. Meta-analysis of the clinical characteristics and prognostic relevance of NOTCH1 and FBXW7 mutation in T-cell acute lymphoblastic leukemia. Oncotarget 2017;8:66360-70.

16. Moharram SA, Shah K, Kazi JU. T-cell Acute Lymphoblastic Leukemia Cells Display Activation of Different Survival Pathways. J Cancer 2017;8:4124.

17. Demarest RM, Ratti F, Capobianco AJ. It’s T-ALL about Notch. Oncogene 2008;27:5082-91.

18. Natarajan V, Bandapalli OR, Rajkumar T, et al. NOTCH1 and FBXW7 mutations favor better outcome in pediatric South Indian T-cell acute lymphoblastic leukemia. J Pediatr Hematol Oncol 2015;37:e23-30.

19. Herranz D, Ferrando AA. Targeting NOTCH1 in T-ALL: Starving the dragon. Cell Cycle 2016;15:483-4.

20. Pear WS, Aster JC. T cell acute lymphoblastic leukemia/lymphoma: a human cancer commonly associated with aberrant NOTCH1 signaling. Curr Opin Hematol 2004;11:426-33.

21. Bray SJ. Notch signalling in context. Nat Rev Mol Cell Biol 2016;17:722-35.

22. Callens C, Baleydier F, Lengline E, et al. Clinical impact of NOTCH1 and/or FBXW7 mutations, FLASH deletion, and TCR status in pediatric T-cell lymphoblastic lymphoma. J Clin Oncol 2012;30:1966-73.

23. Pomari E, Lovisa F, Carraro E, et al. Clinical impact of miR-223 expression in pediatric T-Cell lymphoblastic lymphoma. Oncotarget 2017;8:107886-98.

24. Gallo Llorente L, Luther H, Schneppenheim R, et al. Identification of novel NOTCH1 mutations: increasing our knowledge of the NOTCH signaling pathway. Pediatr Blood Cancer 2014;61:788-96.

25. Bandapalli OR, Zimmermann M, Kox C, et al. NOTCH1 activation clinically antagonizes the unfavorable effect of PTEN inactivation in BFM-treated children with precursor T-cell acute lymphoblastic leukemia.

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26. Hales EC, Taub JW, Matherly LH. New insights into Notch1 regulation of the PI3K-AKT-mTOR1 signaling axis: targeted therapy of gamma-secretase inhibitor resistant T-cell acute lymphoblastic leukemia. Cell Signal 2014;26:149-61.

27. Tetzlaff MT, Yu W, Li M, et al. Defective cardiovascular development and elevated cyclin E and Notch proteins in mice lacking the Fbw7 F-box protein. Proc Natl Acad Sci U S A 2004;101:3338-45.

28. Hoelzer D, Gokbuget N. T-cell lymphoblastic lymphoma and T-cell acute lymphoblastic leukemia: a separate entity? Clin Lymphoma Myeloma 2009;9 Suppl 3:S214-21.

29. Yuan L, Lu L, Yang Y, et al. Genetic mutational profiling analysis of T-cell acute lymphoblastic leukemia reveal mutant FBXW7 as a prognostic indicator for inferior survival. Ann Hematol 2015;94:1817-28.

30. Guo X, Zhang R, Ge Z, et al. Mutations of FBXW7 in Adult T-Cell Acute Lymphocytic Leukemia. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2015;23:612-8.

31. Kox C, Zimmermann M, Stanulla M, et al. The favorable effect of activating NOTCH1 receptor mutations on long-term outcome in T-ALL patients treated on the ALL-BFM 2000 protocol can be separated from FBXW7 loss of function. Leukemia 2010;24:2005-13.

32. Breit S, Stanulla M, Flohr T, et al. Activating NOTCH1 mutations predict favorable early treatment response and long-term outcome in childhood precursor T-cell lymphoblastic leukemia. Blood 2006;108:1151-7.

33. Park MJ, Taki T, Oda M, et al. FBXW7 and NOTCH1 mutations in childhood T cell acute lymphoblastic leukaemia and T cell non-Hodgkin lymphoma. Br J Haematol 2009;145:198-206.

34. Fogelstrand L, Staffas A, Wasslavik C, et al. Prognostic implications of mutations in NOTCH1 and FBXW7 in childhood T-ALL treated according to the NOPHO ALL-1992 and ALL-2000 protocols. Pediatr Blood Cancer 2014;61:424-30.

35. Erbilgin Y, Sayitoglu M, Hatirmaz O, et al. Prognostic significance of NOTCH1 and FBXW7 mutations in pediatric T-ALL. Dis Markers 2010;28:353-60.
38. Zuurbier L, Homminga I, Calvert V, et al. NOTCH1 and/or FBXW7 mutations predict for initial good prednisone response but not for improved outcome in pediatric T-cell acute lymphoblastic leukemia patients treated on DCOG or COALL protocols. Leukemia 2010;24:2014-22.

39. Li J, Yen C, Liaw D, et al. PTEN, a putative protein tyrosine phosphatase gene mutated in human brain, breast, and prostate cancer. Science 1997;275:1943-7.

40. Steck PA, Pershouse MA, Jasser SA, et al. Identification of a candidate tumour suppressor gene, MMAC1, at chromosome 10q23.3 that is mutated in multiple advanced cancers. Nat Genet 1997;15:356-62.

41. You D, Xin J, Volk A, et al. FAK mediates a compensatory survival signal parallel to PI3K-AKT in PTEN-null T-ALL cells. Cell Rep 2015;10:2055-68.

42. Mendes RD, Cante-Barrett K, Pieters R, et al. The relevance of PTEN-AKT in relation to NOTCH1-directed treatment strategies in T-cell acute lymphoblastic leukemia. Haematologica 2016;101:1010-7.

43. Sakai A, Thieblemont C, Wellmann A, et al. PTEN gene alterations in lymphoid neoplasms. Blood 1998;92:3410-5.

44. Shan X, Czar MJ, Bunnell SC, et al. Deficiency of PTEN in Jurkat T cells causes constitutive localization of Itk to the plasma membrane and hyperresponsiveness to CD3 stimulation. Mol Cell Biol 2000;20:6945-57.

45. Xu Z, Stokoe D, Kane LP, et al. The inducible expression of the tumor suppressor gene PTEN promotes apoptosis and decreases cell size by inhibiting the PI3K/Akt pathway in Jurkat T cells. Cell Growth Differ 2002;13:285-96.

46. Balbach ST, Makarova O, Bonn BR, et al. Proposal of a genetic classifier for risk group stratification in pediatric T-cell lymphoblastic lymphoma reveals differences from adult T-cell lymphoblastic leukemia. Cancer Res 1998;58:2618-23.

47. Jenkinson S, Kirkwood AA, Goulden N, et al. PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. Leukemia 2016;30:970-3.

48. Jenkinson S, Kirkwood AA, Goulden N, et al. Impact of PTEN abnormalities on outcome in pediatric patients with T-cell acute lymphoblastic leukemia treated on the MRC UKALL2003 trial. Leukemia 2016;30:970-3.

49. Zuurbier L, Homminga I, Calvert V, et al. NOTCH1 and/or FBXW7 mutations predict for initial good prednisone response but not for improved outcome in pediatric T-cell acute lymphoblastic leukemia patients treated on DCOG or COALL protocols. Leukemia 2010;24:2014-22.

50. Mendes RD, Sarmento LM, Cante-Barrett K, et al. PTEN microdeletions in T-cell acute lymphoblastic leukemia are caused by illegitimate RAG-mediated recombination events. Blood 2014;124:567-78.

51. Trinquand A, Tanguy-Schmidt A, Ben Abdelali R, et al. Toward a NOTCH1/FBXW7/RAS/PTEN-based oncogenic risk classification of adult T-cell acute lymphoblastic leukemia: a Group for Research in Adult Acute Lymphoblastic Leukemia study. J Clin Oncol 2013;31:4333-42.

52. Palomero T, Dominguez M, Ferrando AA. The role of the PTEN/AKT Pathway in NOTCH1-induced leukemia. Cell Cycle 2008;7:965-70.

53. Palomero T, Sulis ML, Cortina M, et al. Mutational loss of PTEN induces resistance to NOTCH1 inhibition in T-cell leukemia. Nat Med 2007;13:1203-10.

54. Burkhardt B, Moericke A, Klapper W, et al. Pediatric precursor T lymphoblastic leukemia and lymphoblastic lymphoma: Differences in the common regions with loss of heterozygosity at chromosome 6q and their prognostic impact. Leuk Lymphoma 2008;49:451-61.

55. Burkhardt B, Bruch J, Zimmermann M, et al. Loss of heterozygosity on chromosome 6q14–24 is associated with poor outcome in children and adolescents with T-cell lymphoblastic lymphoma. Leukemia 2006;20:1422-9.

56. Rohde M, Bonn BR, Zimmermann M, et al. Multiplex ligation-dependent probe amplification validates LOH6q analyses and enhances insight into chromosome 6q aberrations in pediatric T-cell lymphoblastic leukemia and lymphoma. Leuk Lymphoma 2015;56:1884-7.

57. Takeuchi S, Koike M, Seriu T, et al. Frequent loss of heterozygosity on the long arm of chromosome 6: identification of two distinct regions of deletion in childhood acute lymphoblastic leukemia. Cancer Res 1998;58:2618-23.

58. Bonn BR, Rohde M, Zimmermann M, et al. Incidence and prognostic relevance of genetic variations in T-cell lymphoblastic lymphoma in childhood and adolescence. Blood 2013;121:3153-60.

59. Mancini M, Vegna ML, Castoldi GL, et al. Partial deletions of long arm of chromosome 6: biologic and clinical implications in adult acute lymphoblastic leukemia. Leukemia 2002;16:2055-61.

60. Juárez-Velázquez R, Reyes-Leon A, Salas-Labadia C, et al. Significance of CASP8AP2 and H2AFZ expression in survival and risk of relapse in children with acute lymphoblastic leukemia. Leuk Lymphoma 2014;55:2305-11.

61. Liu FF, Wang KL, Deng LP, et al. Transcription factor E2F3a regulates CASP8AP2 transcription and
enhances sensitivity to chemotherapeutic drugs in acute lymphoblastic leukemia. Cancer Cell Int 2018;18:40.
62. Barcaroli D, Dinsdale D, Neale MH, et al. FLASH is an essential component of Cajal bodies. Proc Natl Acad Sci U S A 2006;103:14802-7.
63. Choi YH, Kim KB, Kim HH, et al. FLASH coordinates NF-kappa B activity via TRAF2. J Biol Chem 2001;276:25073-7.
64. Flotho C, Coustan-Smith E, Pei D, et al. Genes contributing to minimal residual disease in childhood acute lymphoblastic leukemia: prognostic significance of CASP8AP2. Blood 2006;108:1050-7.
65. Jiao Y, Cui L, Gao C, et al. CASP8AP2 is a promising prognostic indicator in pediatric acute lymphoblastic leukemia. Leuk Res 2012;36:67-71.
66. Mei Y, Li Z, Zhang Y, et al. Low miR-210 and CASP8AP2 expression is associated with a poor outcome in pediatric acute lymphoblastic leukemia. Oncol Lett 2017;14:8072-7.
67. Lee KD, Pai MY, Hsu CC, et al. Targeted Casp8AP2 methylation increases drug resistance in mesenchymal stem cells and cancer cells. Biochem Biophys Res Commun 2012;422:578-85.
68. Cui L, Gao C, Zhang RD, et al. Low expressions of ARS2 and CASP8AP2 predict relapse and poor prognosis in pediatric acute lymphoblastic leukemia patients treated on China CCLG-ALL 2008 protocol. Leuk Res 2015;39:115-23.
69. Gu Y, Pan Y, Meng B, et al. High levels of bcl-2 protein expression do not correlate with genetic abnormalities but predict worse prognosis in patients with lymphoblastic lymphoma. Tumour Biol 2013;34:1441-50.
70. Kanungo A, Medeiros LJ, Abruzzo LV, et al. Lymphoid neoplasms associated with concurrent t(14;18) and 8q24/ c-MYC translocation generally have a poor prognosis. Mod Pathol 2006;19:25-33.
71. Subramaniam S, Fraser CR, Rao PH, et al. De novo B lymphoblastic leukemia/lymphoma in an adult with t(14;18)(q32;q21) and c-MYC gene rearrangement involving 10p13. Leuk Lymphoma 2011;52:2195-9.
72. Zhang XD, He LM, Ma L, et al. C-MYC Gene and Protein Expression in Paraffin Wax of T Lymphoblastic Lymphoma and Leukemia Patients and Its Effect on the Prognosis. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2018;26:141-5.
73. Wu Y, Tang HY, Ding YY, et al. Value of CD, MPO, Ki-67 and C-MYC Positive Rate in the Pathological Tissues and C-MYC Gene of Patients with T-LBL/ALL for Predicting Prognosis. Zhongguo Shi Yan Xue Ye Xue Za Zhi 2018;26:110-5.
74. Kim MS, Chung NG, Kim MS, et al. Somatic mutation of IL7R exon 6 in acute leukemias and solid cancers. Hum Pathol 2013;44:531-5.
75. Shochat C, Tal N, Bandapalli OR, et al. Gain-of-function mutations in interleukin-7 receptor-alpha (IL7R) in childhood acute lymphoblastic leukemias. J Exp Med 2011;208:901-8.
76. Peschon JJ, Morrissey PJ, Grabstein KH, et al. Early lymphocyte expansion is severely impaired in interleukin 7 receptor-deficient mice. J Exp Med 1994;180:1955-60.
77. Zenatti PP, Ribeiro D, Li W, et al. Oncogenic IL7R gain-of-function mutations in childhood T-cell acute lymphoblastic leukemia. Nat Genet 2011;43:932-9.
78. Puel A, Ziegler SF, Buckley RH, et al. Defective IL7R expression in T(-)B(+)NK(+) severe combined immunodeficiency. Nat Genet 1998;20:394-7.
79. Mansour MR, Reed C, Eisenberg AR, et al. Targeting oncogenic interleukin-7 receptor signalling with N-acetylcysteine in T cell acute lymphoblastic leukaemia. Br J Haematol 2015;168:230-8.
80. Ribeiro D, Melao A, Barata JT. IL-7R-mediated signaling in T-cell acute lymphoblastic leukemia. Adv Biol Regul 2013;53:211-22.
81. Irving J, Matheson E, Minto L, et al. Ras pathway mutations are prevalent in relapsed childhood acute lymphoblastic leukemia and confer sensitivity to MEK inhibition. Blood 2014;124:3420-30.
82. Ariës IM, van den Dungen RE, Koudijs MJ, et al. Towards personalized therapy in pediatric acute lymphoblastic leukemia: RAS mutations and prednisolone resistance. Haematologica 2015;100:e132-6.
83. Li Y, Buijs-Gladdines JG, Cante-Barrett K, et al. IL-7 Receptor Mutations and Steroid Resistance in Pediatric T cell Acute Lymphoblastic Leukemia: A Genome Sequencing Study. PLoS Med 2016;13:e1002200.
84. Canté-Barrett K, Spijkers-Hagelstein JA, Buijs-Gladdines JG, et al. MEK and PI3K-AKT inhibitors synergistically block activated IL7 receptor signaling in T-cell acute lymphoblastic leukemia. Leukemia 2016;30:1832-43.
85. Passtoors WM, van den Akker EB, Deelen J, et al. IL7R gene expression network associates with human healthy ageing. Immun Ageing 2015;12:21.
86. Ben Abdelali R, Asnafi V, Petit A, et al. The prognosis of CALM-AF10-positive adult T-cell acute lymphoblastic leukemias depends on the stage of maturation arrest. Haematologica 2013;98:1711-7.
87. Conway AE, Haldeman JM, Wechsler DS, et al. A critical
role for CRM1 in regulating HOXA gene transcription in CALM-AF10 leukemias. Leukemia 2015;29:423-32.
88. Mulaw MA, Krause A, Deshpande AJ, et al. CALM/AF10-positive leukemias show upregulation of genes involved in chromatin assembly and DNA repair processes and of genes adjacent to the breakpoint at 10p12. Leukemia 2012;26:1012-9.
89. Conway AE, Scotland PB, Lavau CP, et al. A CALM-derived nuclear export signal is essential for CALM-AF10-mediated leukemogenesis. Blood 2013;121:4758-68.
90. Caudell D, Aplan PD. The role of CALM-AF10 gene fusion in acute leukemia. Leukemia 2008;22:678-85.
91. Kroon E, Krosl J, Thorsteinsdottir U, et al. Hoxa9 transforms primary bone marrow cells through specific collaboration with Meis1a but not Pbx1b. EMBO J 1998;17:3714-25.
92. Suzuki M, Yamagata K, Shino M, et al. Nuclear export signal within CALM is necessary for CALM-AF10-induced leukemia. Cancer Sci 2014;105:315-23.
93. Lo Nigro L, Mirabile E, Tumino M, et al. Detection of PICALM-MLLT10 (CALM-AF10) and outcome in children with T-lineage acute lymphoblastic leukemia. Leukemia 2013;27:2419-21.
94. Bohlander SK, Muschinsky V, Schrader K, et al. Molecular analysis of the CALM/AF10 fusion: identical rearrangements in acute myeloid leukemia, acute lymphoblastic leukemia and malignant lymphoma patients. Leukemia 2000;14:93-9.
95. Carlson KM, Vignon C, Bohlander S, et al. Identification and molecular characterization of CALM/AF10 fusion products in T cell acute lymphoblastic leukemia and acute myeloid leukemia. Leukemia 2013;27:2419-21.
96. Heath JL, Weiss JM, Lavau CP, et al. Effects of iron depletion on CALM-AF10 leukemias. Exp Hematol 2014;42:1022-30.e1.
97. Heath JL, Weiss JM, Lavau CP, et al. Iron deprivation in cancer--potential therapeutic implications. Nutrients 2013;5:2836-59.
98. Rowley JD. The role of chromosome translocations in leukemogenesis. Semin Hematol 1999;36:59-72.
99. Carrasco Salas P, Fernandez L, Vela M, et al. The role of CDKN2A/B deletions in pediatric acute lymphoblastic leukemia. Pediatr Hematol Oncol 2016;33:415-22.
100. Agarwal M, Bakhshi S, Dwivedi SN, et al. Cyclin dependent kinase inhibitor 2A/B gene deletions are markers of poor prognosis in Indian children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2018;65:e27001.
101. Beroukhim R, Mermel CH, Porter D, et al. The landscape of somatic copy-number alteration across human cancers.

Nature 2010;463:899-905.
102. ShahidSales S, Mehramiz M, Ghasemi F, et al. A genetic variant in CDKN2A/B gene is associated with the increased risk of breast cancer. J Clin Lab Anal 2018. doi: 10.1002/jcla.22190.
103. Krieger D, Moericke A, Oschlies I, et al. Frequency and clinical relevance of DNA microsatellite alterations of the CDKN2A/B, ATM and p53 gene loci: a comparison between pediatric precursor T-cell lymphoblastic lymphoma and T-cell lymphoblastic leukemia. Haematologica 2010;95:158-62.
104. Bertin R, Acquaviva C, Mirebeau D, et al. CDKN2A, CDKN2B, and MTAP gene dosage permits precise characterization of mono- and bi-allelic 9p21 deletions in childhood acute lymphoblastic leukemia. Genes Chromosomes Cancer 2003;37:44-57.
105. Othman MA, Melo JB, Carreira IM, et al. High rates of submicroscopic aberrations in karyotypically normal acute lymphoblastic leukemia. Mol Cytogenet 2015;8:45.
106. Mirebeau D, Acquaviva C, Suci S, et al. The prognostic significance of CDKN2A, CDKN2B and MTAP inactivation in B-lineage acute lymphoblastic leukemia of childhood. Results of the EORTC studies 58881 and 58951. Haematologica 2006;91:881-5.
107. Roman-Gomez J, Jimenez-Velasco A, Castillejo JA, et al. Promoter hypermethylation of cancer-related genes: a strong independent prognostic factor in acute lymphoblastic leukemia. Blood 2004;104:2492-8.
108. Gupta SK, Bakhshi S, Kumar L, et al. Gene copy number alteration profile and its clinical correlation in B-cell acute lymphoblastic leukemia. Leuk Lymphoma 2017;58:333-42.
109. Xu N, Li YL, Zhou X, et al. CDKN2 Gene Deletion as Poor Prognosis Predictor Involved in the Progression of Adult B-Lineage Acute Lymphoblastic Leukemia Patients. J Cancer 2015;6:1114-20.
110. Rivandi M, Khorrami MS, Fiuji H, et al. The 9p21 locus: A potential therapeutic target and prognostic marker in breast cancer. J Cell Physiol 2018;233:1709-0.
111. Bahrami A, Hassanian SM, Khazaeri M, et al. The 9p21 locus as a potential therapeutic target and prognostic marker in colorectal cancer. Pharmacogenomics 2018;19:463-74.

Cite this article as: Yu H, Du Y, Xu J, Zhang M. Prognostic relevance of genetic variations in T-cell acute lymphoblastic leukemia/lymphoblastic lymphoma. Transl Cancer Res 2019;8(6):2485-2495. doi: 10.21037/tcr.2019.10.04