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儿童急性B淋巴细胞白血病的分子特征及临床意义

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摘　要

儿童急性淋巴细胞白血病是儿童时期最常见的血液恶性肿瘤，虽然病因研究已进行多年，但其在遗传水平上仍是一种异质性疾病。近年来随着测序技术的进步，遗传特征得到更深入的阐述。本文即从儿童急性B淋巴细胞白血病的常见分子特征进行简要概述，并讨论了它们对临床的影响。

关键词

急性淋巴细胞白血病，遗传特征，临床意义

Molecular Characteristics and Clinical Significance of Acute B-Cell Acute Lymphoblastic Leukemia in Children

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Abstract

Acute lymphoblastic leukemia is the most common hematologic malignancy in children. Although the etiology has been studied for a long time, it is still a heterogeneous disease at the genetic level. While with the development of sequencing technology in recent years, genetic characteristics have been further elaborated. In this article, the common molecular characteristics of acute B-cell lymphoblastic leukemia in children are briefly summarized, and their clinical effects are discussed.

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Keywords

Acute Lymphoblastic Leukemia, Genetic Characteristics, Clinical Effects

1. 引言

儿童急性淋巴细胞白血病(Acute lymphoblastic leukemia, ALL)是一种以不成熟的淋巴细胞异常增殖为特征的恶性血液肿瘤疾病，约占儿童急性白血病的 75%~80% [1]。随着危险程度调整、化疗方案优化、支持治疗积极、干细胞移植及嵌合抗原受体T细胞免疫疗法等的发展，其五年总生存率已接近90% [2] [3]。虽然在儿科患者中生存率已较前大大提升，但仍有 10%~20%的患儿复发[4]，复发后则生存率明显降低。目前常规化疗的强度和毒性已达上限，因此，为了提高患儿的生存率及减少不良反应，有必要寻找新的解决途径和方法。病因研究目前包括病毒感染、杀虫剂、苯及衍生物等化学因素、电离辐射、遗传异常等，但在遗传水平上其仍是一种异质性疾病。而近十年来测序技术的进步，使得我们能够检测分子变化，让识别新亚型、做出早期诊断、调整风险分层、进行精准治疗及预后预测成为可能。本文即概述了儿童最常见的急性淋巴细胞白血病－急性 B 淋巴细胞白血病(B-ALL)的分子特征，并讨论了它们的临床意义。

2. BCR-ABL1 融合基因和 Ph-like ALL

BCR-ABL1 融合基因由 9 号染色体的 ABL1 基因(q34 区域)和 22 号染色体的 BCR 基因(q11 区域)易位形成，具有酪氨酸激酶活性，占儿童 ALL 的 3%~5%。因最初在美国费城发现，故发生 t (9; 22) (q34; q11)的染色体也被称为费城(Philadephia, Ph)染色体。Ph 阳性 ALL 患者中较常见的伴随遗传改变是 IKZF1、PAX5 和 EBF1、CDKN2A/2B 基因的缺失，约占 Ph 阳性患者的 80%、50%、14%、50% [5] [6] [7] [8]。有研究指出，CDKN2A/B 缺失与患者预后较差有关[8]，其缺失可能导致耐药。在引入酪氨酸激酶抑制剂(TKIs)治疗之前，Ph 阳性 ALL 患儿预后差、存活率低[9]，在首次完全缓解时接受强化化疗，然后进行造血干细胞移植(HSCT)，是改善预后的唯一机会。TKIs 联合化疗则改变了 Ph 阳性 ALL 患者的预后[10] [11]。长期使用伊马替尼联合适当的化疗可显著延长 EFS 和 OS，且与单纯使用化疗和 TIK 相比，联合使用 CR1 中的 HSCT 巩固并不能提供更好的生存期。而 TKI 单药治疗患儿较易出现 ABL1 激酶结构域的突变(最常见的是 T315I)，从而诱导 TKI 耐药[12]，因此，TIK 联合强化治疗是有必要的，达沙替尼或 ABL 第二代 TKI 联合化疗是儿童 Ph 阳性 ALL 的有效靶向治疗策略[13]。缓解 BCR-ABL1 ALL 不良预后的治疗方法还包括第三代 TKI 帕纳替尼和化疗的一线治疗[14] [15]。

Ph-like ALL 缺乏 BCR-ABL1 基因融合，但显示出与 BCR-ABL1 ALL 相似的基因表达特征，在儿童 ALL 中发生率约为 10% [16]。患儿诱导失败风险较高，MRD 阳性，复发率较高，总生存率较低。IKZF1 高频率改变(70%至 80%)在 Ph 样 ALL 中也不少见，包括整个位点、外显子亚群或上游基因的缺失等异常，使其获得干细胞特性，导致异常白血病细胞粘附，并诱导 TKI 耐药。大约 30%的 Ph-like B-ALL 患者中存在 PAX5 基因改变，并常与 IKZF1 突变同时发生[17]。CRLF2 重排同样常见于 Ph 样 B-ALL 患者中，由于重排导致的 CRLF2 过表达与不良预后相关[18] [19] [20]。即使 MRD 水平较低，CRLF2 过表达伴 IKZF1 缺失也与复发风险增加相关。Ph-like ALL 的大量周期性重排，主要导致激酶编码基因与伴侣基因

的融合[16] [21]。大量相关基因涉及 JAK-STAT 通路、ABL 类融合、Ras 通路突变等改变，可激活细胞因子受体和激酶信号通路。因 Ph-like ALL 的异质性基因组改变和不同的可靶向激酶激活改变需要精确的治疗管理，常规化疗通常效果不佳，致使患儿的最佳治疗方法仍未确定。但激酶通路的一致激活意味着激酶抑制剂可能是这类患者的一种治疗选择。ABL 重排患者最常用 ABL1 抑制剂伊马替尼和 ABL1/SRC 双抑制剂达沙替尼治疗[16] [22] [23]。变异型 ATF7IP-PDGFRB 融合患者，其预后较差，达沙替尼也可成功治疗[24] [25]。JAK1/JAK2 抑制剂鲁索利替尼治疗耐受性良好，可诱导形态学缓解，被认为是治疗 JAK-STAT 激活突变最有效的方法[22]。JAK2 抑制剂也可用于治疗 CRLF2 重排患者[26]。因此，JAK 抑制剂联合化疗可改善这种高危 ALL 亚型患者的预后。如推广前瞻性筛查策略，识别高危患者，早期实施基于 TKI 的干预，有望改善 Ph-like ALL 患儿的结局。

3. ETV6/RUNX1 融合基因和 ETV6-RUNX1-Like ALL

T (12; 21) (p13; q22)易位形成 ETS 转录因子 6 (ETV6，又称 TEL)与 Runt 相关转录因子 1 (RUNX1，也称为 AML1)的基因融合，在儿童 ALL 患儿中约占 20%~25% [27] [28]，是儿童 B-ALL 中最常见的易位，通常与良好预后相关[29]。ETV6 和 RUNX1 都具有编码转录因子的能力，在造血中都起着至关重要的作用。二者融合之后，AML1 由转录活化因子转变为抑制因子是此类白血病的分子基础。脐带血中 ETV6-RUNX1 融合的存在表明这种改变可能起源于产前[28]，是白血病发生过程中的首次打击，而诱导白血病发生需要较长的潜伏期和继发性遗传畸变，因为在健康儿童中也可检测到这种改变[30] [31]。二次打击除 PAX5、ATF7IP、KMT2A 畸变等改变外，还包括 ETV6 非易位等位基因的 12p 的缺失等[32]。在 21 三体患者中，正常 21 号染色体的复制会导致一个额外的 RUNX1 等位基因，可见于 78%的复发患者和 15%的初诊患者，表明 RUNX1 的额外拷贝以及 21 号染色体的重复可能与较差的预后相关。ETV6-RUNX1 融合属于有利风险遗传学组，具有良好的疗效[33]。但也有研究指出 ETV6-RUNX1 重排的儿童 ALL 与常见的晚期复发有关[34]，然而复发后针对第二次完全缓解的治疗是有效的，甚至疗效更高。有研究表明，ETV6-RUNX1 重排 ALL 患者良好的初始 MRD 反应和减量治疗强调了良好的结果，使其可能受益于化疗强度的降低，而较长的疗程可能被认为是决定预后的最重要因素之一，因为大多数复发发生在治疗后[35]。

近期，有研究指出 ETV6-RUNX1-like ALL 这种新的亚型，其发生率约为 ALL 患儿的 2%~3%。尽管缺乏 ETV6-RUNX1 基因融合，但它具有相似的基因表达谱和免疫表型(CD27 阳性，CD44 低至阴性)。先前的研究表明 ETV6-RUNX1-like 亚型具有相对较好的预后，很少有复发报道[36]。但近期研究证明其由于 MRD 水平高和无事件生存率差，预后不良[37]。ETV6-RUNX1-like 亚型可能受益于更高强度的治疗[38]。但由于该类型 ALL 患者数量较少，该领域仍需更多研究。

4. KMT2A 重排(MLL)

赖氨酸甲基转移酶 2A (KMT2A，既往被称为混合谱系白血病-MLL)基因位于染色体 11q23 上，其相关易位导致 KMT2A 与超过 90 个不同的伴侣基因融合[39]，在 ALL 患儿中发生率为 5%，但在婴儿白血病中发生率却能达到 70%~80%。T (4; 11) (q21; q23)易位形成 KMT2A-AFF1(以前称为 KMT2A-AF4)，约占 KMT2A 重排 ALL 婴儿的 41%，预后很差；次常见的是 t (11; 19) (q23; p13.3)易位形成的 KMT2A-MLLT1 (以前为 KMT2A-ENL)，第三常见的是 t (9; 11) (p22; q23)易位形成的 KMT2A-MLLT3 (以前称为 KMT2A-AF9) [40]。婴儿 ALL 中的其他主要伴侣基因还包括 MLLT10 (原 AF10)和 MLLT4 (原 AF6)等。研究表明，内含子 11 中存在 KMT2A 断点的患者预后较差，KMT2A 重排的婴儿预后特别差。尽管婴儿 ALL 患者协同突变的总体数量较低，但酪氨酸激酶、PI3K、RAS 信号通路的突变频率较高，包括 KRAS

和 NRAS 中的复发性突变，以及 FLT3、NF1 和 PTPN11 中的非复发性突变[41]。且在婴儿中，KMT2A 重排急性白血病更有可能伴有高白细胞和中枢神经系统疾病[42]。小鼠遗传模型显示 Dot1L (端粒沉默干扰体 1)在 KMT2A 重排 ALL 的启动和维持中起着重要作用。可能包括 AF9、ENL 和 AF10 在内的 KMT2A 易位伙伴的表达，依赖于将过多的 DOT1L 活性招募到它们的目标位点，因此使用 Dot1L 抑制剂可能是一种有前途的靶向治疗方法[43]。其他潜在的治疗靶点包括溴结构域、menin、BCL-2 抑制剂等[39] [43] [44]。

5. TCF3 重排

转录因子 3，又称 TCF3 或 E2A，在淋巴细胞生成中起着重要作用，是 T 和 B 淋巴细胞正常发育和分化所必需的。T (1; 19) (q23; p13.3)易位，在成人和儿童 B-ALL 患者中总发生率为 5%~6%，会产生 TCF3-PBX1 基因融合，产生嵌合蛋白，干预造血调控过程[45] [46]。研究发现与其他 B-ALL 亚型相比，t (1; 19) B-ALL 细胞中 ROR1 和 Wnt16b 过表达，表明 Wnt16b-ROR1 在这些细胞中可能存在共同的信号通路[47]。恶性 B 细胞中 ROR1 高表达，通过自分泌或旁分泌结合 Wnt5a，与非典型 Wnt 通路的激活有关，可调节细胞增殖、趋化性和存活。在 TCF3-PBX1 细胞中过表达 ROR1 可能是一种有前景的靶向治疗策略，以减少对正常 B 淋巴细胞的细胞毒性作用[48]。由于中枢神经系统受累和复发较高[47] [49]，TCF3-PBX1 融合被认为是预后不好的标志。但由于化疗方案的调整，患儿预后较前改善[50] [51]，因此，该亚型现在被认为是有利或中间型。TCF3-PBX1 融合基因阳性的小鼠白血病表现出肿瘤抑制基因(PAX5 和 CDKN2A/2B)的持续缺失和点突变后(JAK/STAT, RAS/MAPK)信号通路的激活，表明达沙替尼、鲁索利替尼、帕纳替尼靶向治疗的可能性[48]。T (17; 19) (q22; p13)易位会引发 TCF3-HLF 融合，在儿童 B-ALL 中发生率不足 1%。其预后极差，尽管进行强化治疗和 HSCT，但失败率很高，通常会复发且在诊断后两年内死亡[52]。预后差，病例少，导致这些患者缺乏特定的化疗方案。BCL20 抑制剂维奈托克可作为潜在的治疗因子[52]，甲基化分析提示 KBTBD11 可能是其潜在靶点[53]，CAR-T 疗法也似乎是改善缓解率的一种有前途的治疗方式[54]。

6. 其他

IKZF1 位于 7 号染色体的 p12.2，转录后能产生不同大小的 IKAROS 蛋白异构体，与 DNA 高效结合，对淋巴系细胞特别是 B 淋巴细胞的增殖分化等起着关键作用[55] [56]。B-ALL 患儿中 IKZF1 缺失频率估计为 16%~27%。IKAROS 缺陷则抑制前体 B 淋巴细胞，使其易于恶性转化[57]。目前发现，IKZF1 的改变常见于 BCR-ABL1 阳性 ALL 和 BCR-ABL1 样 ALL 中。BCR-ABL1 阳性 ALL 的改变可能导致对酪氨酸激酶抑制剂治疗的耐药性，并导致治疗结果较差[58]。相比之下，在 TCF3 重排和 ETV6-RUNX1 阳性 B-ALL 中很少检测到 IKZF1 缺失[59]。IKZF1 异常的 B-ALL 患者 5 年 EFS 和总生存期降低，复发风险更高[60]。最近，IKZF1 plus 亚型也被发现，其特征是在没有 ERG 缺失的情况下，IKZF1 缺失与 CDKN2A、CDKN2B、PAX5 或 PAR1 中的缺失共存。较 IKZF1 缺失型患者，IKZF1 plus 有更差的预后[60]。IKZF1 功能障碍也可能导致 PI3K、AKT、mTOR 通路的激活，进而促进对 ALL 患者基本治疗药物糖皮质激素的耐药[61]。因此，IKZF1 基因改变在儿童 B-ALL 的发病机制和不良预后中都有重要作用，应纳入儿童 B-ALL 治疗早期风险分层的研究中。

PAX5 位于 9p13 染色体上，通过激活 B 细胞特异性基因诱导 B 细胞分化，是 B 细胞发育早期阶段的关键调节因子。此外，它还负责通过 PD-1 和 NOTCH1 转录因子的负调控和 M-CSFR 抑制从而抑制向其他细胞系的进展。PAX5 局限在 B 细胞中表达，其表达的任何变化都可能导致白血病发生并引发恶性肿瘤[62]。作为儿童 B-ALL 体细胞突变最重要的靶点，其突变被认为是 B-ALL 最常见的遗传变异之一。PAX5alt 存在于 7%~10%的儿童 B-ALL 病例中，包括重排、局灶性/基因内扩增或突变等不同的改变，是

高危风险指标之一[36]。PAX5 P80R 在儿童患者中发生率则为 3%~4%，可能伴随着 CDKN2A 的双等位基因缺失、表观遗传因子 SETD2 的突变失活以及野生型 PAX5 等位基因的失活。而 PAX P80R 与包括 Ras、JAK/STAT、FLT3 在内的信号通路共突变的存在，则为靶向治疗创造了可能[63]。由于基因的高度异质性，PAX 驱动的亚型可能需要不同的治疗药物，如化疗和多种抑制剂的组合，以及免疫治疗[64]。

CDKN2A (细胞周期蛋白依赖性激酶抑制物 2A)基因，也称为 INK4A 或 P16-INK4A，位于 9 号染色体 p21.3，其最常见的基因变化是缺失，可见于约 25%的 ALL 患者。过去研究大多认为 CDKN2A 缺失是儿童 ALL 预后的不良因素[65] [66] [67]，但少数研究也认为 CDKN2A 可能是良好的预后指标[68]。由于反复出现的 9p 缺失，它们通常与 PAX5 缺失同时发生[69]。在 Ph 阳性和 Ph 样 ALL 患者中也可发现，而在 ETV6-RUNX1 中则较少发现。在 B-ALL 中，杂合子和纯合子 CDKN2A 缺失似乎以相近的频率发生[17] [70] [71]。然而，基于聚合酶链反应(PCR)和免疫细胞化学等方法进行缺失检测，则无法检测出杂合缺失。一些研究表明双等位基因和单等位基因突变都会影响患者的预后[70]。然而，一些研究表明，只有纯合子缺失才会对患者的监测产生临床影响[72]。INK4 蛋白调节功能的破坏可导致 CDK4/CDK6 活性增加，导致不受控制的增殖。目前进行的 CDK4/CDK6 药物抑制剂的临床试验，如帕博西尼、瑞博西尼和阿贝西利，它们可以阻断 G1 期的细胞周期，并可能防止白血病进展[73] [74] [75]。

目前，随着治疗水平的提高和新技术的发展，我们已发现越来越多的新亚型，且测序技术的进一步发展，使我们有望检测出新的遗传标记，从而更好地理解其分子基础、进行危险度分层调整、检测疾病进程、协助判断预后并尽可能降低化疗毒副作用。同时，分子水平的研究也对研发新的靶向治疗和细胞免疫疗法等新治疗方法提供可能。全面了解遗传缺陷特征，为儿童 ALL 的精准医疗提供了更广阔的前景。然而，是否对白血病遗传易感性进行广泛筛查值得商榷，因为一些带有 ALL 特定基因变异的儿童并不会发展为临床 ALL，潜在假阳性预测值较大。

参考文献

[1] 王凯玲, 梅妍妍, 崔蕾, 高超, 刘飞飞, 赵晓曦, 等. 两种化疗方案对于 TEL-AML1 融合基因阳性儿童急性淋巴细胞白血病的疗效比较[J]. 中国实验血液学杂志, 2014, 22(2): 285-290.

[2] Capria, S., Molica, M., Mohamed, S., *et al*. (2020) A Review of Current Induction Strategies and Emerging Prognostic Factors in the Management of Children and Adolescents with Acute Lymphoblastic Leukemia. *Expert Review of Hematology*, **13**, 755-769. https://doi.org/10.1080/17474086.2020.1770591

[3] Inaba, H. and Pui, C.-H. (2021) Advances in the Diagnosis and Treatment of Pediatric Acute Lymphoblastic Leukemia. *Journal of Clinical Medicine*, **10**, 1926. https://doi.org/10.3390/jcm10091926

[4] Abdelmabood, S., Fouda, A.E., Boujettif, F. and Mansour, A. (2020) Treatment Outcomes of Children with Acute Lymphoblastic Leukemia in a Middle-Income Developing Country: High Mortalities, Early Relapses, and Poor Survival. *The Journal of Pediatrics* (*Rio J*), **96**, 108-116. https://doi.org/10.1016/j.jped.2018.07.013

[5] Bernt, K.M. and Hunger, S.P. (2014) Current Concepts in Pediatric Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. *Frontiers in Oncology*, **4**, 54. https://doi.org/10.3389/fonc.2014.00054

[6] Mullighan, C.G., Miller, C.B., Radtke, I., Phillips, L.A., Dalton, J., Ma, J., *et al*. (2008) BCR-ABL1 Lymphoblastic Leukaemia Is Characterized by the Deletion of Ikaros. *Nature*, **453**, 110-114. https://doi.org/10.1038/nature06866

[7] Iacobucci, I., Lonetti, A., Paoloni, F., *et al*. (2010) The PAX5 Gene Is Frequently Rearranged in BCR-ABL1-Positive Acute Lymphoblastic Leukemia but Is Not Associated with Outcome. A Report on Behalf of the GIMEMA Acute Leukemia Working Party. *Haematologica*, **95**, 1683-1690. https://doi.org/10.3324/haematol.2009.020792

[8] Notta, F., Mullighan, C.G., Wang, J.C.Y., Poeppl, A., Doulatov, S., Phillips, L.A., *et al*. (2011) Evolution of Human BCR-ABL1 Lymphoblastic Leukaemia-Initiating Cells. *Nature*, **469**, 362-367. https://doi.org/10.1038/nature09733

[9] Churchman, M.L. and Mullighan, C.G. (2017) Ikaros: Exploiting and Targeting the Hematopoietic Stem Cell Niche in B-Progenitor Acute Lymphoblastic Leukemia. *Experimental Hematology*, **46**, 1-8. https://doi.org/10.1016/j.exphem.2016.11.002

[10] Mizuta, S., Matsuo, K., Yagasaki, F., Yujiri, T., Hatta, Y., Kimura, Y., *et al*. (2011) Pre-Transplant Imatinib-Based Therapy Improves the Outcome of Allogeneic Hematopoietic Stem Cell Transplantation for BCR-ABL-Positive Acute

Lymphoblastic Leukemia. *Leukemia*, **25**, 41-47. https://doi.org/10.1038/leu.2010.228

[11] Jing, Y., Chen, H.R., Liu, M.J., *et al*. (2014) Susceptibility of Ph-Positive All to TKI Therapy Associated with Bcr-Abl Rearrangement Patterns: A Retrospective Analysis. *PLOS ONE*, **9**, e110431. https://doi.org/10.1371/journal.pone.0110431

[12] Chang, B.H., Willis, S.G., Stork, L., Hunger, S.P., Carroll, W.L., Camitta, B.M., *et al*. (2012) Imatinib Resistant BCR-ABL1 Mutations at Relapse in Children with Ph+ ALL: A Children's Oncology Group (COG) Study. *British Journal of Haematology*, **157**, 507-510. https://doi.org/10.1111/j.1365-2141.2012.09039.x

[13] Cerchione, C., Locatelli, F. and Martinelli, G. (2021) Dasatinib in the Management of Pediatric Patients with Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. *Frontiers in Oncology*, **11**, Article ID: 632231. https://doi.org/10.3389/fonc.2021.632231

[14] Dalle, I.A., Jabbour, E., Short, N.J. and Ravandi, F. (2019) Treatment of Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia. *Current Treatment Options in Oncology*, **20**, 4. https://doi.org/10.1007/s11864-019-0603-z

[15] 曹文静, 李硕敏. BCR-ABL1 激酶抑制剂的疗效与耐药机制研究进展[J]. 肿瘤药学, 2020, 10(6): 641-648.

[16] Roberts, K.G., Li, Y.J., Payne-Turner, D., Harvey, R.C., Yang, Y.-L., Pei, D.Q., *et al*. (2014) Targetable Kinase-Activating Lesions in Ph-Like Acute Lymphoblastic Leukemia. *The New England Journal of Medicine*, **371**, 1005-1015. https://doi.org/10.1056/NEJMoa1403088

[17] Ou, Z.S., Sherer, M., Casey, J., Bakos, H.A., Vitullo, K., Hu, J., *et al*. (2016) The Genomic Landscape of PAX5, IKZF1, and CDKN2A/B Alterations in B-Cell Precursor Acute Lymphoblastic Leukemia. *Cytogenetic and Genome Research*, **150**, 242-252. https://doi.org/10.1159/000456572

[18] Roberts, K.G., Pei, D., Campana, D., Payne-Turner, D., Li, Y.J., Cheng, C., *et al*. (2014) Outcomes of Children with BCR-ABL1-Like Acute Lymphoblastic Leukemia Treated with Risk-Directed Therapy Based on the Levels of Minimal Residual Disease. *Journal of Clinical Oncology*, **32**, 3012-3020. https://doi.org/10.1200/JCO.2014.55.4105

[19] Heatley, S.L., Sadras, T., Kok, C.H., Nievergall, E., Quek, K., Dang, P., *et al*. (2017) High Prevalence of Relapse in Children with Philadelphia-Like Acute Lymphoblastic Leukemia Despite Risk-Adapted Treatment. *Haematologica*, **102**, e490-e493. https://doi.org/10.3324/haematol.2016.162925

[20] 张钰, 吴秉毅. CRLF2 基因在 B 系急性淋巴细胞白血病中的研究进展[J]. 广东医学, 2017, 38(S1): 292-294.

[21] Roberts, K.G., Morin, R.D., Zhang, J.H., Hirst, M., Zhao, Y.J., Su, X.P., *et al*. (2012) Genetic Alterations Activating Kinase and Cytokine Receptor Signaling in High-Risk Acute Lymphoblastic Leukemia. *Cancer Cell*, **22**, 153-166. https://doi.org/10.1016/j.ccr.2012.06.005

[22] Roberts, K.G., Yang, Y.-L., Payne-Turner, D., Lin, W.W., Files, J.K., Dickerson, K., *et al*. (2017) Oncogenic Role and Therapeutic Targeting of ABL-Class and JAK-STAT Activating Kinase Alterations in Ph-Like ALL. *Blood Advances*, **1**, 1657-1671.

[23] Iacobucci, I., Li, Y.J., Roberts, K.G., Dobson, S.M., Kim, J.C., Payne-Turner, D., *et al*. (2016) Truncating Erythropoietin Receptor Rearrangements in Acute Lymphoblastic Leukemia. *Cancer Cell*, **29**, 186-200. https://doi.org/10.1016/j.ccell.2015.12.013

[24] Kobayashi, K., Miyagawa, N., Mitsui, K., Matsuoka, M., Kojima, Y., Takahashi, H., *et al*. (2015) TKI Dasatinib Monotherapy for a Patient with Ph-Like ALL Bearing ATF7IP/PDGFRB Translocation. *Pediatric Blood & Cancer*, **62**, 1058-1060. https://doi.org/10.1002/pbc.25327

[25] Zhang, G., Zhang, Y.L., Wu, J.R., Chen, Y. and Ma, Z.G. (2017) Acute Lymphoblastic Leukemia Patient with Variant ATF7IP/PDGFRB Fusion and Favorable Response to Tyrosine Kinase Inhibitor Treatment: A Case Report. *American Journal of Case Reports*, **18**, 1204-1208. https://doi.org/10.12659/AJCR.906300

[26] Reshmi, S.C., Harvey, R.C., Roberts, K.G., *et al*. (2017) Targetable Kinase Gene Fusions in High-Risk B-ALL: A Study from the Children's Oncology Group. *Blood*, **129**, 3352-3361. https://doi.org/10.1182/blood-2016-12-758979

[27] Sundaresh, A. and Williams, O. (2017) Mechanism of ETV6-RUNX1 Leukemia. *Advances in Experimental Medicine and Biology*, **962**, 201-216. https://doi.org/10.1007/978-981-10-3233-2_13

[28] Shurtleff, S.A., Buijs, A., Behm, F.G., Rubnitz, J.E., Raimondi, S.C., Hancock, M.L., *et al*. (1995) TEL/AML1 Fusion Resulting from a Cryptic t(12;21) Is the Most Common Genetic Lesion in Pediatric ALL and Defines a Subgroup of Patients with an Excellent Prognosis. *Leukemia*, **9**, 1985-1989.

[29] Rubnitz, J.E., Wichlan, D., Devidas, M., Shuster, J., Linda, S.B., Kurtzberg, J., *et al*. (2008) Prospective Analysis of TEL Gene Rearrangements in Childhood Acute Lymphoblastic Leukemia: A Children's Oncology Group Study. *Journal of Clinical Oncology*, **26**, 2186-2191. https://doi.org/10.1200/JCO.2007.14.3552

[30] Andreasson, P., Schwaller, J., Anastasiadou, E., Aster, J. and Gilliland, D.G. (2001) The Expression of ETV6/CBFA2 (TEL/AML1) Is Not Sufficient for the Transformation of Hematopoietic Cell Lines *in Vitro* or the Induction of Hematologic Disease *in Vivo*. *Cancer Genetics and Cytogenetics*, **130**, 93-104.

https://doi.org/10.1016/S0165-4608(01)00518-0

[31] Morrow, M., Horton, S., Kioussis, D., Brady, H.J.M. and Williams, O. (2004) TEL-AML1 Promotes Development of Specific Hematopoietic Lineages Consistent with Preleukemic Activity. *Blood*, **103**, 3890-3896. https://doi.org/10.1182/blood-2003-10-3695

[32] Cavé, H., Cacheux, V., Raynaud, S., Brunie, G., Bakkus, M., Cochaux, P., *et al*. (1997) ETV6 Is the Target of Chromosome 12p Deletions in t(12;21) Childhood Acute Lymphocytic Leukemia. *Leukemia*, **11**, 1459-1464. https://doi.org/10.1038/sj.leu.2400798

[33] McLean, T.W., Ringold, S., Neuberg, D., Stegmaier, K., Tantravahi, R., Ritz, J., *et al*. (1996) TEL/AML-1 Dimerizes and Is Associated with a Favorable Outcome in Childhood Acute Lymphoblastic Leukemia. *Blood*, **88**, 4252-4258. https://doi.org/10.1182/blood.V88.11.4252.bloodjournal88114252

[34] 王邢玮, 李本尚, 沈树红, 陈静, 汤静燕, 等. ETV6/RUNX1 阳性儿童急性 B 系淋巴细胞白血病临床预后研究[J]. 临床儿科杂志, 2016, 34(5): 321-325.

[35] Wang, Y., Zeng, H.-M. and Zhang, L.-P. (2018) ETV6/RUNX1-Positive Childhood Acute Lymphoblastic Leukemia in China: Excellent Prognosis with Improved BFM Protocol. *Italian Journal of Pediatrics*, **44**, 94. https://doi.org/10.1186/s13052-018-0541-6

[36] Gu, Z.H., Churchman, M.L., Roberts, K.G., Moore, I., Zhou, X., Nakitandwe, J., *et al*. (2019) PAX5-Driven Subtypes of B-Progenitor Acute Lymphoblastic Leukemia. *Nature Genetics*, **51**, 296-307. https://doi.org/10.1038/s41588-018-0315-5

[37] Jeha, S., Choi, J., Roberts, K.G., Pei, D.Q., Coustan-Smith, E., Inaba, H., *et al*. (2021) Clinical Significance of Novel Subtypes of Acute Lymphoblastic Leukemia in the Context of Minimal Residual Disease-Directed Therapy. *Blood Cancer Discovery*, **2**, 326-337. https://doi.org/10.1158/2643-3230.BCD-20-0229

[38] Lee, S.H.R., Li, Z.H., Tai, S.T., Oh, B.L.Z. and Yeoh, A.E.J. (2021) Genetic Alterations in Childhood Acute Lymphoblastic Leukemia: Interactions with Clinical Features and Treatment Response. *Cancers* (*Basel*), **13**, 4068. https://doi.org/10.3390/cancers13164068

[39] Winters, A.C. and Bernt, K.M. (2017) MLL-Rearranged Leukemias—An Update on Science and Clinical Approaches. *Frontiers in Pediatrics*, **5**, 4. https://doi.org/10.3389/fped.2017.00004

[40] Jansen, M.W.J.C., Corral, L., van der Velden, V.H.J., Panzer-Grümayer, R., Schrappe, M., Schrauder, A., *et al*. (2007) Immunobiological Diversity in Infant Acute Lymphoblastic Leukemia Is Related to the Occurrence and Type of MLL Gene Rearrangement. *Leukemia*, **21**, 633-641. https://doi.org/10.1038/sj.leu.2404578

[41] Andersson, A.K., Ma, J., Wang, J.M., Chen, X., Gedman, A.L., Dang, J.J., *et al*. (2015) The Landscape of Somatic mutations in Infant MLL-Rearranged Acute Lymphoblastic Leukemias. *Nature Genetics*, **47**, 330-337. https://doi.org/10.1038/ng.3230

[42] Tauchi, H., Tomizawa, D., Eguchi, M., *et al*. (2008) Clinical Features and Outcome of MLL Gene Rearranged Acute Lymphoblastic Leukemia in Infants with Additional Chromosomal Abnormalities Other than 11q23 Translocation. *Leukemia Research*, **32**, 1523-1529. https://doi.org/10.1016/j.leukres.2008.03.018

[43] Chen, C.-W., Koche, R.P., Sinha, A.U., Deshpande, A.J., Zhu, N., Eng, R., *et al*. (2015) DOT1L Inhibits SIRT1-Mediated Epigenetic Silencing to Maintain Leukemic Gene Expression in MLL-Rearranged Leukemia. *Nature Medicine*, **21**, 335-343. https://doi.org/10.1038/nm.3832

[44] Klossowski, S., Miao, H.Z., Kempinska, K., Wu, T., Purohit, T., Kim, E., *et al*. (2020) Menin Inhibitor MI-3454 Induces Remission in MLL1-Rearranged and NPM1-Mutated Models of Leukemia. *Journal of Clinical Investigation*, **130**, 981-997. https://doi.org/10.1172/JCI129126

[45] Aspland, S.E., Bendall, H.H. and Murre, C. (2001) The Role of E2A-PBX1 in Leukemogenesis. *Oncogene*, **20**, 5708-5717. https://doi.org/10.1038/sj.onc.1204592

[46] Diakos, C., Xiao, Y.Y., Zheng, S.C., Kager, L., Dworzak, M. and Wiemels, J.L. (2014) Direct and Indirect Targets of the E2A-PBX1 Leukemia-Specific Fusion Protein. *PLOS ONE*, **9**, e87602. https://doi.org/10.1371/journal.pone.0087602

[47] Jeha, S., Pei, D., Raimondi, S.C., Onciu, M., Campana, D., Cheng, C., *et al*. (2009) Increased Risk for CNS Relapse in Pre-B Cell Leukemia with the t(1;19)/TCF3-PBX1. *Leukemia*, **23**, 1406-1409. https://doi.org/10.1038/leu.2009.42

[48] Bicocca, V.T., Chang, B.H., Masouleh, B.K., Muschen, M., Loriaux, M.M., Druker, B.J., *et al*. (2012) Crosstalk between ROR1 and the Pre-B Cell Receptor Promotes Survival of t(1;19) Acute Lymphoblastic Leukemia. *Cancer Cell*, **22**, 656-667. https://doi.org/10.1016/j.ccr.2012.08.027

[49] Crist, W.M., Carroll, A.J., Shuster, J.J., Behm, F.G., Whitehead, M., Vietti, T.J., *et al*. (1990) Poor Prognosis of Children with pre-B Acute Lymphoblastic Leukemia Is Associated with the t(1;19)(q23;p13): A Pediatric Oncology Group Study. *Blood*, **76**, 117-122. https://doi.org/10.1182/blood.V76.1.117.117

[50] Lin, A., Cheng, F.W.T., Chiang, A.K.S., Luk, C.-W., Li, R.C.H., Ling, A.S.C., *et al*. (2018) Excellent Outcome of Acute Lymphoblastic Leukaemia with TCF3-PBX1 Rearrangement in Hong Kong. *Pediatric Blood & Cancer*, **65**, e27346. https://doi.org/10.1002/pbc.27346

[51] Wang, Y., Xue, Y.-J., Lu, A.-D., Jia, Y.-P., Zuo, Y.-X., Zhang, L.-P., *et al*. (2021) Long-Term Results of the Risk-Stratified Treatment of TCF3-PBX1-Positive Pediatric Acute Lymphoblastic Leukemia in China. *Clinical Lymphoma, Myeloma and Leukemia*, **21**, e137-e144. https://doi.org/10.1016/j.clml.2020.09.009

[52] Fischer, U., Forster, M., Rinaldi, A., Risch, T., Sungalee, S., Warnatz, H.-J., *et al*. (2015) Genomics and Drug Profiling of Fatal TCF3-HLF-Positive Acute Lymphoblastic Leukemia Identifies Recurrent Mutation Patterns and Therapeutic Options. *Nature Genetics*, **47**, 1020-1029. https://doi.org/10.1038/ng.3362

[53] Kachroo, P., Szymczak, S., Heinsen, F.-A., Forster, M., Bethune, J., Hemmrich-Stanisak, G., *et al*. (2018) NGS-Based Methylation Profiling Differentiates TCF3-HLF and TCF3-PBX1 Positive B-Cell Acute Lymphoblastic Leukemia. *Epigenomics*, **10**, 133-147. https://doi.org/10.2217/epi-2017-0080

[54] Wang, T.Y., Wan, X.Y., Yang, F., Shi, W.H., Liu, R., Ding, L.X., *et al*. (2021) Successful Treatment of TCF3-HLF-Positive Childhood B-ALL with Chimeric Antigen Receptor T-Cell Therapy. *Clinical Lymphoma, Myeloma and Leukemia*, **21**, 386-392. https://doi.org/10.1016/j.clml.2021.01.014

[55] Stanulla, M., Cavé, H. and Moorman, A.V. (2020) IKZF1 Deletions in Pediatric Acute Lymphoblastic Leukemia: Still a Poor Prognostic Marker? *Blood*, **135**, 252-260. https://doi.org/10.1182/blood.2019000813

[56] Marke, R., van Leeuwen, F.N. and Scheijen, B. (2018) The Many Faces of IKZF1 in B-Cell Precursor Acute Lymphoblastic Leukemia. *Haematologica*, **103**, 565-574. https://doi.org/10.3324/haematol.2017.185603

[57] Joshi, I., Yoshida, T., Jena, N., *et al*. (2014) Loss of Ikaros DNA-Binding Function Confers Integrin-Dependent Survival on pre-B Cells and Progression to Acute Lymphoblastic Leukemia. *Nature Immunology*, **15**, 294-304. https://doi.org/10.1038/ni.2821

[58] van der Veer, A., Zaliova, M., Mottadelli, F., De Lorenzo, P., Te Kronnie, G., Harrison, C.J., *et al*. (2014) IKZF1 Status as a Prognostic Feature in BCR-ABL1-Positive Childhood All. *Blood*, **123**, 1691-1698. https://doi.org/10.1182/blood-2013-06-509794

[59] Sulong, S., Moorman, A.V., Irving, J.A.E., Strefford, J.C., Konn, Z.J., Case, M.C., *et al*. (2009) A Comprehensive Analysis of the CDKN2A Gene in Childhood Acute Lymphoblastic Leukemia Reveals Genomic Deletion, Copy Number Neutral Loss of Heterozygosity, and Association with Specific Cytogenetic Subgroups. *Blood*, **113**, 100-107. https://doi.org/10.1182/blood-2008-07-166801

[60] Stanulla, M., Dagdan, E., Zaliova, M., Möricke, A., Palmi, C., Cazzaniga, G., *et al*. (2018) IKZF1(plus) Defines a New Minimal Residual Disease-Dependent Very-Poor Prognostic Profile in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. *Journal of Clinical Oncology*, **36**, 1240-1249. https://doi.org/10.1200/JCO.2017.74.3617

[61] Piovan, E., Yu, J.Y., Tosello, V., Herranz, D., Ambesi-Impiombato, A., Carolina Da Silva, A., *et al*. (2013) Direct Reversal of Glucocorticoid Resistance by AKT Inhibition in Acute Lymphoblastic Leukemia. *Cancer Cell*, **24**, 766-776. https://doi.org/10.1016/j.ccr.2013.10.022

[62] Shahjahani, M., Norozi, F., Ahmadzadeh, A., Shahrabi, S., Tavakoli, F., Asnafi, A.A., *et al*. (2015) The Role of Pax5 in Leukemia: Diagnosis and Prognosis Significance. *Medical Oncology*, **32**, 360. https://doi.org/10.1007/s12032-014-0360-6

[63] Novakova, M., Zaliova, M., Fiser, K., Vakrmanova, B., Slamova, L., Musilova, A., *et al*. (2021) DUX4r, ZNF384r and PAX5-P80R Mutated B-Cell Precursor Acute Lymphoblastic Leukemia Frequently Undergo Monocytic Switch. *Haematologica*, **106**, 2066-2075. https://doi.org/10.3324/haematol.2020.250423

[64] Li, J.F., Dai, Y.T., Wu, L., Zhang, M., Ouyang, W., Huang, J.Y., *et al*. (2021) Emerging Molecular Subtypes and Therapeutic Targets in B-Cell Precursor Acute Lymphoblastic Leukemia. *Frontiers in Medicine*, **15**, 347-371. https://doi.org/10.1007/s11684-020-0821-6

[65] Zhang, W.H., Kuang, P. and Liu, T. (2019) Prognostic Significance of CDKN2A/B Deletions in Acute Lymphoblastic Leukaemia: A Meta-Analysis. *Annals of Medicine*, **51**, 28-40. https://doi.org/10.1080/07853890.2018.1564359

[66] Agarwal, M., Bakhshi, S., Dwivedi, S.N., *et al*. (2018) Cyclin Dependent Kinase Inhibitor 2A/B Gene Deletions Are Markers of Poor Prognosis in Indian Children with Acute Lymphoblastic Leukemia. *Pediatric Blood & Cancer*, **65**, e27001. https://doi.org/10.1002/pbc.27001

[67] Kathiravan, M., Singh, M., Bhatia, P., Trehan, A., Varma, N., Sachdeva, M.S., *et al*. (2019) Deletion of CDKN2A/B Is Associated with Inferior Relapse Free Survival in Pediatric B Cell Acute Lymphoblastic Leukemia. *Leukemia & Lymphoma*, **60**, 433-441. https://doi.org/10.1080/10428194.2018.1482542

[68] Karrman, K., Castor, A., Behrendtz, M., *et al*. (2015) Deep Sequencing and SNP Array Analyses of Pediatric T-Cell Acute Lymphoblastic Leukemia Reveal NOTCH1 Mutations in Minor Subclones and a High Incidence of Uniparental Isodisomies Affecting CDKN2A. *Journal of Hematology Oncology*, **8**, 42. https://doi.org/10.1186/s13045-015-0138-0

[69] Steeghs, E.M.P., Boer, J.M., Hoogkamer, A.Q., Boeree, A., de Haas, V., de Groot-Kruseman, H.A., *et al*. (2019) Copy Number Alterations in B-Cell Development Genes, Drug Resistance, and Clinical Outcome in Pediatric B-Cell Precursor Acute Lymphoblastic Leukemia. *Scientific Reports*, **9**, 4634. https://doi.org/10.1038/s41598-019-41078-4

[70] Feng, J., Guo, Y., Yang, W.Y., Zou, Y., Zhang, L., Chen, Y.M., *et al*. (2022) Childhood Acute B-Lineage Lymphoblastic Leukemia with CDKN2A/B Deletion Is a Distinct Entity with Adverse Genetic Features and Poor Clinical Outcomes. *Frontiers in Oncology*, **12**, Article ID: 878098. https://doi.org/10.3389/fonc.2022.878098

[71] Kim, M.Y., Yim, S.-H., Cho, N.-S., Kang, S.-H., Ko, D.-H., Oh, B., *et al*. (2009) Homozygous Deletion of CDKN2A (p16, p14) and CDKN2B (p15) Genes Is a Poor Prognostic Factor in Adult but Not in Childhood B-Lineage Acute Lymphoblastic Leukemia: A Comparative Deletion and Hypermethylation Study. *Cancer Genetics and Cytogenetics*, **195**, 59-65. https://doi.org/10.1016/j.cancergencyto.2009.06.013

[72] Salas, P.C., Fernández, L., Vela, M., Bueno, D., González, B., Valentín, J., *et al*. (2016) The Role of CDKN2A/B Deletions in Pediatric Acute Lymphoblastic Leukemia. *Pediatric Hematology and Oncology*, **33**, 415-422. https://doi.org/10.1080/08880018.2016.1251518

[73] Sawai, C.M., Freund, J., Oh, P., Ndiaye-Lobry, D., Bretz, J.C, Strikoudis, A., *et al*. (2012) Therapeutic Targeting of the Cyclin D3:CDK4/6 Complex in T Cell Leukemia. *Cancer Cell*, **22**, 452-465. https://doi.org/10.1016/j.ccr.2012.09.016

[74] Sheppard, K.E. and McArthur, G.A. (2013) The Cell-Cycle Regulator CDK4: An Emerging Therapeutic Target in Melanoma. *Clinical Cancer Research*, **19**, 5320-5328. https://doi.org/10.1158/1078-0432.CCR-13-0259

[75] Dickson, M.A. (2014) Molecular Pathways: CDK4 Inhibitors for Cancer Therapy. *Clinical Cancer Research*, **20**, 3379-3383. https://doi.org/10.1158/1078-0432.CCR-13-1551