Characterization of TCF3 rearrangements in pediatric B-lymphoblastic leukemia/lymphoma by mate-pair sequencing (MPseq) identifies complex genomic rearrangements and a novel TCF3/TEF gene fusion

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Abstract

The TCF3/PBX1 gene fusion is a recurrent genetic abnormality in pediatric B-lymphoblastic leukemia/lymphoma (B-ALL/LBL). While dual-color, dual-fusion fluorescence in situ hybridization (D-FISH) probes can detect TCF3/PBX1 fusions, further characterization of atypical TCF3 FISH patterns as indicated by additional or diminished TCF3 signals is currently limited. Herein we describe the use of a next-generation sequencing assay, mate-pair sequencing (MPseq), to characterize typical and cryptic TCF3/PBX1 fusions and to identify TCF3 translocation partners based on results obtained from our laboratory-developed TCF3/PBX1 D-FISH probe set. MPseq was performed on 21 cases of pediatric B-ALL/LBL with either TCF3/PBX1 fusion, or no TCF3/PBX1 fusion but with additional or diminished TCF3 signals obtained by our PBX1/TCF3 D-FISH probe set. In addition, MPseq was performed on one pediatric B-ALL/LBL case with an apparently normal karyotype and abnormal TCF3 break-apart probe results. Of 22 specimens successfully evaluated by MPseq, 13 cases (59%) demonstrated TCF3/PBX1 fusion, including three cases with previously undescribed insertional rearrangements. The remaining nine cases (41%) harbored various TCF3 partners, including six cases with TCF3/ZNF384, and one case each with TCF3/HLF, TCF3/FLI1 and TCF3/TEF. Our results illustrate the power of MPseq to characterize TCF3 rearrangements with increased precision and accuracy over traditional cytogenetic methodologies.

Introduction

Rearrangements involving the TCF3 (previously known as E2A) gene region (19p13.3) are common in both pediatric and adult B-lymphoblastic leukemia/lymphoma (B-ALL/LBL) and account for ~6% of newly diagnosed cases1–4. The PBX1 gene (1q23) is the most common translocation partner for TCF3, resulting in TCF3/PBX1 gene fusion, and is currently classified in the WHO as a recurrent genetic abnormality in B-ALL/LBL4. Fusion of TCF3/PBX1 is usually generated from a reciprocal t(1;19) (q23;p13.3) and results in a 5′TCF3/3′PBX1 fusion gene located on the der(19)t(1;19) chromosome4–6. Interestingly, the majority of 1;19 translocations (~80%) only present with the der(19)t(1;19) as observed by conventional chromosome and/or fluorescence in situ hybridization (FISH) studies5. Several rare TCF3 gene fusion
partners have been described, most commonly ZNF384 (12p13) and HLF (17q21). Since highly variable prognoses are associated with the various TCF3 translocation partners (TCF3/HLF fusion has an extremely poor prognosis in contrast to the favorable/standard risk for TCF3/PBX1 fusion), the characterization of TCF3 partners is essential.

To detect the recurrent TCF3/PBX1 gene fusion in B-ALL/LBL, our laboratory developed and validated a dual-color, dual-fusion FISH (D-FISH) TCF3/PBX1 probe set for clinical application. To further characterize TCF3/PBX1 fusions associated with discordant chromosome results and the TCF3 rearrangements with additional or diminished TCF3 signals obtained by our TCF3/PBX1 D-FISH probe set, we utilized a next-generation sequencing (NGS) strategy, mate-pair sequencing (MPseq). This novel NGS-based technology enables the characterization of chromosomal rearrangements with significantly higher resolution and precision compared to conventional cytogenetic methodologies, including chromosome and FISH studies. Herein, we report conventional chromosome, FISH and the molecular characterization of each TCF3 rearrangement by MPseq. Details regarding probe development and performance have been previously described.

Materials and methods

Patient selection

Following institutional review board approval, a retrospective review of the Mayo Clinic cytogenetic database was performed to identify bone marrow samples with abnormal results evaluated by our TCF3/PBX1 D-FISH probe set. Ten pediatric patient cases were chosen that had typical concordant abnormal chromosome and abnormal TCF3/PBX1 fusion D-FISH signal patterns, including six patients with a balanced t(1;19) and a 1R1G2F D-FISH signal pattern (Table 1; patients 1–6), and four patients with an unbalanced der(19)t(1;19) and a 2R1G1F D-FISH signal pattern (Table 1; patients 7–10). In addition, three pediatric patient cases were included with discordant abnormal chromosome results versus D-FISH results (Table 1; patients 11–13). Patients with atypical D-FISH signal patterns including additional or diminished TCF3 signals in the absence of TCF3/PBX1 fusion were also identified, and represent a total of eight cases (Table 1; patients 14–21). One case with an apparently normal female karyotype and TCF3 rearrangement obtained via a TCF3 break-apart probe (BAP) strategy was also included in our study (Table 1; patient 22). In total, 22 cases of pediatric B-ALL/LBL with TCF3 abnormalities detected by FISH were included in our study, and evaluated by MPseq on either fresh or fixed cell pellets from bone marrow aspirate specimens.

Conventional chromosome analysis

Bone marrow aspirate specimens were cultured in unstimulated media, harvested and banded utilizing standard cytogenetic techniques according to specimen-specific protocols. Twenty metaphases were analyzed when available.

Fluorescence in situ hybridization

FISH analysis was performed on bone marrow aspirates specimens following standard FISH pretreatment, hybridization and fluorescence microscopy protocols utilizing a laboratory-developed TCF3/PBX1 D-FISH probe set. Details regarding probe development and performance have been previously described.

Mate-pair sequencing

MPseq was performed using the Illumina Nextera Mate-Pair library protocol (Illumina, San Diego, CA) and sequenced on the Illumina HiSeq 2500. Sequence data were aligned to hg38 using BIMA, and a custom bioinformatics tool was used to filter the alignments and identify junctions. Detailed methods can be found in Drucker et al., Johnson et al., and Smadbeck et al.

Results

Conventional chromosome, FISH, and MPseq results from all 22 patients (age range: 1–16 years) are presented in Table 1. For the 13 patients with TCF3/PBX1 fusion, six cases had a balanced t(1;19) by chromosomes and a double fusion by D-FISH (patients 1–6), four cases had an unbalanced der(19)t(1;19) by chromosomes and a single fusion by D-FISH (patients 7–10), and three cases had seemingly discrepant chromosome and FISH results, indicated by an unbalanced der(19)t(1;19) by chromosomes versus a double fusion signal pattern by D-FISH (patients 11–13). MPseq confirmed the balanced (patients 1–6) and unbalanced (patients 7–10) 1;19 translocations observed by both chromosome and FISH studies. In addition, MPseq revealed insertional rearrangements accounting for the discrepant chromosome and FISH results in the three cases with der(19)t(1;19) and two fusion signals (patients 11–13) (Fig. 1a–e). The MPseq results explained serial metaphase FISH, which had documented TCF3/PBX1 fusion located on a “normal” copy of chromosome 1q in each case, suggesting a cryptic insertional rearrangement.

The nine remaining samples (patients 14–22) had additional or diminished TCF3 signals in the absence of TCF3/PBX1 fusions, and only four of seven cases (patients 14, 17, 18 and 21) with available chromosome studies had abnormalities involving the 19p13 chromosomal region.
Table 1  Conventional cytogenetic, PBX1/TCF3 D-FISH and MPseq results for 22 cases of pediatric B-ALL with TCF3 rearrangements

| Patient | Gender | Age (years) | Karyotype | Interphase PBX1/TCF3 D-FISH signal patterns | Abnormal interphase nuclei (%) | MPseq results | TCF3 fusion partner | Exon fusion (TCF3; partner) |
|---------|--------|-------------|-----------|---------------------------------------------|---------------------------------|---------------|-------------------|-----------------------------|
| 1       | F      | 2           | 46,XX(t;1;19)(q23;p13.3)[1]/46,XX,add(9p13)(pl3p22),del(19)(q13;q22)[2]/46,XY,del(1;22)(q10;q10)[6]/46,XX,add(19)(p13q22)[4]/46,XX[dic(9p13q22)](tcf3x3)PBX1 con TCF3x2 | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 91 | t(1;19) | PBX1 | e16e3 |
| 2       | M      | 2           | 46,XY(t;1;19)(q23;p13.3)[1]/46,XY[9] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 86 | t(1;19) | PBX1 | e16e3 |
| 3       | M      | 5           | 46,XY(t;1;19)(q23;p13.3)[8]/46,XY,del(6),+6,+8,+21,+22[8]/46,XY[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 95 | t(1;19) | PBX1 | e16e3 |
| 4       | M      | 7           | 46,XY(t;1;19)(q23;p13.3)[17]/46,XY[3] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 98 | t(1;19) | PBX1 | e16e3 |
| 5       | M      | 16          | 46,XY(t;1;19)(q23;p13.3)[16]/46,XY[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 92 | t(1;19) | PBX1 | e16e3 |
| 6       | M      | 16          | 46,XY(t;1;19)(q23;p13.3)[15]/46,XY[5] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 96 | t(1;19) | PBX1 | e16e3 |
| 7       | F      | 4           | 46,XX,add(8)(q22),add(9p13),del(9p13p22),der(19)(q13;q22)[2]/46,XY,add(9p13),del(9p13p22),der(19)(q13;q22)[2]/46,XY,del(1;22)(q10;q10)[6]/46,XY,del(1;22)(q10;q10)[6]/46,XY[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 95 | der(19)t(1;19) | PBX1 | e16e3 |
| 8       | M      | 4           | 46,XY,del(19)(q13;q23),del(19)(q13;q23)[2]/46,XY[7] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 98 | der(19)t(1;19) | PBX1 | e16e3 |
| 9       | F      | 9           | 46,XX,del(1;22)(q10;q10),del(1;22)(q10;q10),del(1;22)(q10;q10),del(1;22)(q10;q10)[5]/46,XX,del(1;22)(q10;q10)[5]/46,XX[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 97 | der(19)t(1;19) | PBX1 | e16e3 |
| 10      | F      | 9           | 46,XX,del(1;22)(q10;q10),del(1;22)(q10;q10),del(1;22)(q10;q10),del(1;22)(q10;q10)[5]/46,XX[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 96 | der(19)t(1;19) | PBX1 | e16e3 |
| 11      | M      | 4           | 46,XY,del(19)(q13;q23)[2]/46,XY[7] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 83 | Complex | PBX1 | e16e3 |
| 12      | M      | 8           | 46,XY,del(19)(q13;q23)[2]/46,XY[7] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 72 | Complex | PBX1 | e16e3 |
| 13      | M      | 15          | 46,XY,del(19)(q13;q23)[10]/46,XY[10] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 69 | Complex | PBX1 | e16e3 |
| 14      | F      | 2           | 46,XX(t;16;16)(p13.3q22),add(19)(p13.2)[16]/46,XX[4] | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 56 | t(12;19) | ZNF384 | e13e3 |
| 15      | M      | 6           | NA | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 62 | t(12;19) | ZNF384 | e17e7 |
| 16      | F      | 8           | NA | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 47 | t(12;19) | ZNF384 | e13e3 |
| 17      | F      | 13          | NA | (PBX1,TCF3)x3(PBX1 con TCF3)x2 | 33 | t(12;19) | ZNF384 | e13e3 |
Among these nine cases, MPseq detected variant TCF3 gene partners, including six cases with ZNF384 (patients 14–19) (Fig. 2a–d), and one case each with the following three genes: TEF (patient 20) (Fig. 3a–c), FLI1 (patient 21) and HLF (patient 22). Moreover, MPseq indicated all rearrangements were predicted to create in-frame gene–gene fusions, including all three potential TCF3 exons (14–16) described in patient 22.

Discussion

Herein, we demonstrate the ability for MPseq to molecularly characterize 22 B-ALL/LBL specimens that were either positive for TCF3/PBX1 fusion or displayed an atypical TCF3 FISH pattern with additional or diminished TCF3 signals obtained by our TCF3/PBX1 D-FISH probe set. Precise identification of these rearrangements is critical as there are significant prognostic differences between TCF3/PBX1 fusion and the less common TCF3/HLF fusion, the latter having a significantly unfavorable prognosis. To our knowledge, this represents only the second report of TCF3/FLI1 fusion in the literature and the first to report TCF3/TEF fusion, although additional follow-up for our patient and identification of the 19;22 translocation and outcomes in other patients are necessary.

Ten pediatric B-ALL/LBL cases with both balanced (patients 1–6) and unbalanced (patients 7–10) TCF3/PBX1 fusions (patients 1–6) and unbalanced (patients 7–10) TCF3/PBX1 fusions (patients 1–6) were readily confirmed by MPseq. In addition, three TCF3/PBX1 D-FISH studies were formally characterized by MPseq, and two patient karyotypes were further characterized by MPseq beyond the capability of traditional chromosome and FISH methodologies. In all three cases, D-FISH studies suggested a typical 1;19 translocation (two fusion signal pattern); however, the conventional FISH fluorescence in situ hybridization, D-FISH dual-color dual-fusion FISH probe set, MPseq mate-pair sequencing

Table 1 continued

| Patient | Gender | Age (years) | Karyotype | Interphase PBX1/TCF3 D-FISH signal patterns | Abnormal interphase nuclei (%) | MPseq results | TCF3 fusion partner | Exon fusion (TCF3; partner) |
|---------|--------|-------------|-----------|---------------------------------------------|-------------------------------|----------------|---------------------|---------------------------|
| 18      | F      | 1           | 46,XX,add(19)(p13.3)[8]/46,ident(5)[q13]+46,XX,add(5)[p11.2]/46,ident(5)[q11.2],add(15)[q22],add(19)[p13.3]+mar[18]/46,XX[2] | (PBX1)x2,TCF3 dimx1,TCF3x1 | 76 | der(19)t | ZNF384 | e11,e3 |
| 19      | M      | 8           | 46,XY,der(3)(pter->3q13.2::3q26.3->3qter),der(9)(9pter->9p22:3q13.2->3q26.3::9p13.2->9qter)[5]/46,X[1] | (PBX1)x2,TCF3 dimx1,TCF3x1 | 77 | der(19)t | ZNF384 | e13,e2 |
| 20      | F      | 3           | 46,XX,add(9)(p22)[2]/46,XX(t(11;12)[p11.2]/46,XX[12] | (PBX1)x2,TCF3x3 | 31 | t(12;19) | TEF | e16,e4 |
| 21      | F      | 10          | 46,XX,der(11)(t;11;9)x23p13.1,add(11)[p11.2]/46,XX[12] | (PBX1)x2,TCF3x3 | 79 | t(11;19) | FLI1 | e16,e6 |
| 22      | F      | 13          | 46,XX[20] | (5′TCF3,3′TCF3x2]5′TCF3 x 3′TCF3x1) | 69 | t(17;19) | HLF | 7e14–16,e4 |
chromosome study in each case identified the more common unbalanced derivative chromosome 1;19 along with two apparently normal copies of chromosome 1. Metaphase FISH studies using the TCF3/PBX1 probe set on the abnormal metaphases demonstrated the expected TCF3/PBX1 fusion on the der(19)t(1;19), while the second TCF3/PBX1 fusion was revealed on one of the apparently normal copies of chromosome 1q at the typical 1q23 location of PBX1, suggesting a potential cryptic insertional rearrangement. MPseq clarified that an ~30–60 kb segment of chromosome 19p was inserted into chromosome 1q, supporting the D-FISH results and resulting in a complex insertion involving two chromosomal regions containing the TCF3/PBX1 fusion. This insertional translocation and the derivative chromosome 19 show only a single breakpoint resulting in TCF3/PBX1 fusion, likely indicating an initial translocation event followed by a secondary “repair” event to restore the karyotypically normal chromosome 1. Alternatively, and less likely, insertional and translocation events with nearly identical breakpoints occurred independently, each resulting in a TCF3/PBX1 fusion.

MPseq also revealed two cryptic TCF3/ZNF384 fusions resulting from unbalanced chromosome 19p translocation events (patients 18 and 19). These cases resulted in ~6 Mb of chromosome 12 material replacing ~2 Mb of chromosome 19 material, a subtle change that is not readily detectable by conventional chromosome analysis. Additionally, since this rearrangement results in the loss of only a portion of the TCF3 probe signal using our t(1;19) D-FISH strategy, the only visible alteration was a diminished TCF3 signal.

In cases with additional TCF3 signals identified by interphase TCF3/PBX1 D-FISH studies, metaphase FISH
may provide low-resolution input into the general chromosomal locus of the TCF3 gene partner. For patients 14, 20 and 21, metaphase FISH localized the additional TCF3 FISH signal to chromosomes 12p, 22q and 11q, respectively. However, for patients 15, 16 and 17, metaphase FISH analysis was not possible due to either absence of metaphases or poor sample quality. Irrespective of metaphase FISH studies, which can at best suggest potential partner genes, MPseq was necessary to characterize each of the TCF3 gene fusion partners in nine cases evaluated in our series, including ZNF384 (patients 14–19), TEF (patient 20), FLI1 (patient 21) and HLF (patient 22).

MPseq therefore represents an advance in the detection of clinically relevant structural rearrangements. While traditional NGS has the potential to detect rearrangements using paired end sequencing, MPseq allows for the characterization of structural rearrangements while requiring a significantly lower depth of coverage. The strength of MPseq lies in the unique library preparation, where long reads (2–5 kb) are circularized and fragmented to allow for their interrogation using traditional NGS. In contrast to basic NGS, where paired end sequencing will give linked reads separated by a few hundred base pairs, the circular MPseq fragments give linked reads much further away from each other (2–5 kb), thus significantly increasing the potential to identify discordant reads.

The ability to assess genome-wide structure down to gene-level resolution makes MPseq a powerful tool for annotating simple and complex structural rearrangements as well as copy number changes, although some limitations exist. Breakpoints occurring within repetitive regions, such as in centromeric or segmental duplication mediated regions are challenging to map. The ability to use overall coverage as a proxy for copy number alleviates this limitation to some extent assuming any repeat-mediated rearrangement is unbalanced. Similarly, its ability to detect terminal rearrangements is also limited since telomeric sequences are also repetitive and difficult to map, and are therefore subject to the same technical challenges. Lastly, the low depth of coverage of MPseq
makes the detection of low level or subclonal rearrangements more challenging, with clonal populations at less than 25 and 10% involvement having reduced sensitivity for copy number and structural rearrangements, respectively. Therefore, MPseq offers the most utility in a diagnostic setting as opposed to monitoring for minimal residual disease. However, as the cost of sequencing continues to decline and instrument output increases, it is likely these limitations could be overcome with increased sequencing depth.

In conclusion, we have presented a 22-patient pediatric B-ALL/LBL cohort with TCF3 rearrangements that have been interrogated by standard cytogenetics, D-FISH for TCF3/PBX1 and MPseq. Our data demonstrate the ability of MPseq to characterize cryptic structural rearrangements associated with discordant chromosome and TCF3/PBX1 FISH results and to identify rare and novel TCF3 gene fusion partners associated with diminished or additional TCF3 FISH signals. We report the identification of a novel TCF3 fusion partner, TEF, by MPseq, and based on the functional similarities to HLF, TEF may represent a second possible unfavorable TCF3 translocation. Overall, MPseq represents a powerful NGS-based technology that allows for further investigation and characterization of structural chromosome rearrangements in hematologic malignancies and will aid in the overall understanding of genomic structural variation.

Acknowledgements
This study was supported by the Mayo Clinic Department of Laboratory Medicine and Pathology.

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R.A.R., J.F.P., and R.P.K. wrote the manuscript; R.A.R., S.A.S., C.M.W., and Y.N. analyzed the raw data; S.A.S., C.M.W., G.V., J.B.S., Y.N., P.T.G., N.L.H., and L.B.B. reviewed and approved the final manuscript.

Conflict of interest
GV: Algorithms described in this manuscript for mate-pair sequencing are licensed to WholeGenome LLC owned by GV.
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Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 27 June 2019 Revised: 13 August 2019 Accepted: 15 August 2019 Published online: 01 October 2019

References
1. Mullighan, C. G. Molecular genetics of B-precursor acute lymphoblastic leukemia. J. Clin. Invest. 122, 3407–3415 (2012).
2. Andersen, M. K. et al. Paediatric B-cell precursor acute lymphoblastic leukaemia with t(1;19)(q23;p13): clinical and cytogentic characteristics of 47 cases from the Nordic countries treated according to NOPHO protocols. Br. J. Haematol. 155, 235–243 (2011).
3. Kager, L. et al. Incidence and outcome of TCF3-PBX1-positive acute lymphoblastic leukaemia in Austrian children. Haematologica 92, 1561–1564 (2007).
4. Swerdlow, S. H. et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues Revised 4th edn. (International Agency for Research on Cancer, Lyon, France, 2017).
5. Paulsson, K., Horvat, A., Fioretos, T., Mitelman, F. & Johansson, B. Formation of an alternative TCF3/PBX1 fusion transcript in t(1;19) (q23:p13)-positive acute lymphoblastic leukaemias. Br. J. Haematol. 138, 196–201 (2007).
6. Zhong, C. H. et al. E2A-ZNF384 and NOL1-E2A fusion created by a cryptic t (12;19)(p13.3; p13.3) in acute lymphoblastic leukemia. Leukemia 22, 723–729 (2008).
7. Barber, K. E. et al. Molecular cytogenetic characterization of TCF3 (E2A)/19p13.3 rearrangements in B-cell precursor acute lymphoblastic leukemia. Genes Chromosomes Cancer 46, 478–486 (2007).
8. Hirabayashi, S. et al. N2F384-related fusion genes define a subgroup of childhood B-cell precursor acute lymphoblastic leukemia with a characteristic immunotype. Haematologica 102, 118–129 (2017).
9. Shearer, B. M., Flynn, H. C., Knudson, R. A. & Ketterling, R. P. Interphase FISH to detect PBX1/E2A fusion resulting from the der(19)(1;19)(q23;p13.3) or t(1;19)(q23;p13.3) in paediatric patients with acute lymphoblastic leukaemia. Br. J. Haematol. 129, 45–52 (2005).
10. Dewald, G. W., Broderick, D. J., Tom, W. W., Hagstrom, J. E. & Pierre, R. V. The efficacy of direct, 24-hour culture, and mitotic synchronization methods for cytogenetic analysis of bone marrow in neoplastic hematologic disorders. Cancer Genet. Cytogenet. 18, 8–10 (1985).
11. Drucker, T. M. et al. BIMA V3: an aligner customized for mate pair library sequencing. Bioinformatics 30, 1627–1629 (2014).
12. Johnson, S. H. et al. SVtools for junction detection of genome-wide chromosomal rearrangements by mate-pair sequencing (MPseq). Cancer Genet. 221, 1–18 (2018).
13. Smadbeck, J. B. et al. Copy number variant analysis using genome-wide mate-pair sequencing. Genes, Chromosomes Cancer 57, 459–470 (2018).
14. Gu, Z. et al. Genomic analyses identify recurrent MEF2D fusions in acute lymphoblastic leukaemia. Nat. Commun. 7, 13331 (2016).
15. Aspland, S. E., Bendall, H. H. & Murre, C. The role of E2A-PBX1 in leukemogenesis. Oncogene 20, 5708–5717 (2001).
16. Seidel, M. G. & Look, A. T. E2A-HLF usurps control of evolutionarily conserved survival pathways. Oncogene 20, 5718–5725 (2001).
17. Hunger, S. P., Li, S., Fall, M. Z., Naumovski, L. & Cleary, M. L. The proto-oncogene HLF and the related basic leucine zipper protein TEF display highly similar DNA-binding and transcriptional regulatory properties. Blood 87, 4607–4617 (1996).
18. Tran, A. N. et al. High-resolution detection of chromosomal rearrangements in leukemias through mate pair genome sequencing. PLoS ONE 13, e0199928 (2018).
19. Aypar, U. et al. Mate pair sequencing improves detection of genomic abnormalities in acute myeloid leukemia. Eur. J. Haematol. 102, 87–96 (2019).