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Clinical and genomic characterization of patients diagnosed with the provisional entity acute myeloid leukemia with *BCR-ABL1*, a Swedish population-based study

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Abstract

Acute myeloid leukemia (AML) with t(9;22)(q34;q11), also known as AML with *BCR-ABL1*, is a rare, provisional entity in the WHO 2016 classification and is considered a high-risk disease according to the European LeukemiaNet 2017 risk stratification. We here present a retrospective, population-based study of this disease entity from the Swedish Acute Leukemia Registry. By strict clinical inclusion criteria we aimed to identify genetic markers further distinguishing AML with t(9;22) as a separate entity. Twenty-five patients were identified and next-generation sequencing using a 54-gene panel was performed in 21 cases. Interestingly, no mutations were found in *NPM1*, *FLT3*, or *DNMT3A*, three frequently mutated genes in AML. Instead, *RUNX1* was the most commonly mutated gene, with aberrations present in 38% of the cases compared to around 10% in *de novo* AML. Additional mutations were identified in genes involved in RNA splicing (*SRSF2*, *SF3B1*) and chromatin regulation (*ASXL1*, *STAG2*, *BCOR*, *BCORL1*). Less frequently, mutations were found in *IDH2*, *NRAS*, *TET2*, and *TP53*. The mutational landscape exhibited a similar pattern as recently described in patients with chronic myeloid leukemia (CML) in myeloid blast crisis (BC). Despite the concomitant presence of *BCR-ABL1* and *RUNX1* mutations in our cohort, both features of high-risk AML, the *RUNX1*-mutated cases showed a superior overall survival compared to *RUNX1* wildtype cases. Our results suggest that the molecular characteristics of AML with t(9;22)/*BCR-ABL1* and CML in myeloid BC are similar and do not support a distinction of the two disease entities based on their underlying molecular alterations.

KEYWORDS

acute myeloid leukemia, *BCR-ABL1*, chronic myeloid leukemia blast crisis, *RUNX1*, t(9;22)

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1 | INTRODUCTION

The t(9;22)(q34;q11), generating the *BCR-ABL1* fusion gene, is the cytogenetic hallmark of chronic myeloid leukemia (CML), but is also recurrently found in high-risk acute lymphoblastic leukemia (ALL) and in approximately 0.5% to 3% of all acute myeloid leukemia (AML) cases.¹⁻⁴ Due to the rarity of AML with t(9;22) and the lack of population-based studies, the true incidence and clinical characteristics of AML with t(9;22) have not been thoroughly characterized. The 2016 WHO classification of myeloid malignancies and acute leukemia includes AML with *BCR-ABL1* as a provisional entity, which is classified as a high risk AML according to European LeukemiaNet (ELN).^{3,5} Still, the distinction between AML with *BCR-ABL1* and CML in myeloid blast crisis (BC) is not clear, and diagnostic challenges have led to an ongoing debate as to whether AML with *BCR-ABL1* represents a distinctive subgroup of AML.^{6,7} Clinical findings supporting the diagnosis of *de novo* AML with *BCR-ABL1* include a lack of history of CML, absence of splenomegaly and absence of peripheral blood basophilia at diagnosis.⁸ A broader genetic characterization is largely lacking or inconclusive. No clinical distinction between the P190 and P210 isoforms of the *BCR-ABL1* rearrangement has been reported and no specific pattern of additional cytogenetic abnormalities has been described, although the occurrence of the t(9;22) in less than 100% of metaphases supports the diagnosis of AML rather than CML.⁸ Loss of *IKZF1* and *CDKN2A* and cryptic deletions in *IGH* and *TRG* have been reported as distinctive for AML with *BCR-ABL1*.⁶ One study reported that *NPM1* mutations were exclusively present in AML with *BCR-ABL1*, while absent in CML in BC.⁹ The outcome of patients with AML with *BCR-ABL1* has only been reported in case reports and small series of heterogeneous patient cohorts.^{7,8,10} Different chemotherapy regimens have been used and remission rates have varied, but in general AML with *BCR-ABL1* seems to be chemotherapy sensitive with relatively high CR rates.^{7,8,10,11} Still, there are limited data available on the molecular and clinical features of this provisional WHO entity. In the present study, we undertook a retrospective population-based study of AML cases with t(9;22) in the Swedish Acute Leukemia Registry. We describe the clinical and genetic characteristics as determined by gene panel sequencing of 21 cases, representing the largest population-based study available to date of AML with t(9;22)/*BCR-ABL1*.

2 | MATERIALS AND METHODS

2.1 | Patient cohort and clinical characterization

The patients were collected from the Swedish Acute Leukemia Registry from January 1997 to December 2015, which includes 6345 patient files, and were selected if the karyotype included t(9;22) with or without additional cytogenetic abnormalities. Thirty-nine patients were identified. After cross-checking with original medical files from the reporting center and with the Swedish CML Registry, 25 patients fulfilling the criteria for AML with t(9;22) remained. Strict diagnostic criteria for AML with *BCR-ABL1* as reported by Soupir *et al*⁷ and Neuendorff *et al*⁸ were used as follows: AML documented by morphology and immunophenotyping; the

presence of t(9;22) in the karyotype; no of history of CML; absence of palpable or radiologically documented splenomegaly; and absence of basophilia in the peripheral blood. In addition, patients were matched to current WHO 2016 and ELN 2017 criteria.^{3,5,7,8} Detailed clinical data for each specific patient were collected according to a case report form (CRF) since the Swedish Acute Leukemia Registry does not include complete information on the disease characteristics. The CRFs included complete blood cell count (CBC), differential blood count, CT scan or ultrasound in order to determine the presence of splenomegaly, clinical examination, performance status, bone marrow (BM) morphology, immunophenotyping, karyotype, chemotherapy with specific schedule, including tyrosine kinase inhibitor (TKI), details about allogeneic stem cell transplantation, conditioning regimens, graft vs host disease (GVHD) prophylaxis and donor lymphocyte infusion (DLI) treatment (Table S1). The CRF was sent to six regional representatives of the Swedish AML Steering Group and the requested data were obtained based on detailed analysis of the medical charts. The completed CRF was sent back to main investigators and analyzed according to the study plan (Table S1). All patients underwent conventional BM morphologic examination and immunophenotyping. The majority of patient samples were also subjected to chromosome banding analysis (G-banding) and reverse transcriptase polymerase chain reaction (RT-PCR) for the detection of *BCR-ABL1* transcripts. This study was approved by the Regional Ethical committee; DNR 2015/260.

2.2 | Next-generation sequencing

High-molecular-weight DNA was extracted from BM cells, peripheral blood, or BM smears using QIAamp DNA Micro Kit (Qiagen, Germany). In total, DNA was obtained from 21 of the 25 cases. Sequencing libraries were prepared from 50 ng DNA using the amplicon based Illumina TruSight Myeloid Sequencing panel, targeting 54 genes or gene-regions, according to the manufacturer's protocol (Illumina, San Diego, CA). Libraries were quantified (Qubit fluorometric quantification, ThermoFisher Scientific, MA) and normalized. Paired 2x151 bp sequencing reads were generated using a NextSeq500 instrument (Illumina). Each library generated at least 3.1 million read-pairs. Paired-end reads were merged with PEAR.¹² The reads were aligned to the human reference genome hg19 using BWA. Somatic single nucleotide variant (SNV) and small indel calling was performed using FreeBayes and mutect2.¹³⁻¹⁵ Pindel was used for detection of smaller (less than 500 bp) structural rearrangements.¹⁶ Retrieved variants were filtered against an in-house database of known technical artefacts and then further filtered to include only protein-altering variants, with a coverage of 500x and a variant allele frequency (VAF) above 15%. The retained variants were subsequently annotated as putative oncogenic based on prior knowledge reported in hematological diseases (Cosmic, OncoKB), recurrence in an in-house clinical database (based on more than 1500 paired normal/control routine clinical cases) and presence below 1% in germline databases (gnomAD). Regions with target coverage below 500x (ie, *CEBPA*) were manually reviewed. One sample (case 10) had a high number of variants

presumed to be technical noise; therefore, only known hotspot mutations were included from this sample.

2.3 | *FLT3*-ITD detection by PCR

Presence of *FLT3*-ITD was also verified by PCR in all but three samples (cases 1, 10, and 17). In short, 100 ng DNA was used with primers targeting the internal tandem duplication (ITD)-region (*FLT3* F, 5' GCA ATT TAG GTA TGA AAG CCA GC 3'; *FLT3* R, 5' CTT TCA GCA TTT TGA CGG CAA CC 3'). The reaction was performed in 50 μ l for 35 cycles and the amplified product was analyzed on a 2100 bioanalyzer (Agilent, CA) DNA 1000 chip. A 329 bp product indicated a wild type (wt) allele and a second, larger product, a mutated allele.

2.4 | Statistics

Clinical data were obtained from the Swedish Acute Leukemia Registry and the Swedish Population Register (FBR-Folkbokföringsregistret). Students *T*-test or Fisher's exact test were used, as deemed appropriate, to compare groups. Differences in survival were calculated using log-rank (Mantel-Cox) tests. Calculations were performed in GraphPad Prism 8 Version 8.4.2.

3 | RESULTS

3.1 | Clinical data

Twenty-five patients from the Swedish Acute Leukemia Registry fulfilled the stringently defined criteria of AML with t(9;22)/*BCR-ABL1* (Table S1). DNA from BM or blood samples at the time of diagnosis was successfully extracted from 21 of these cases. For these 21 patients (38% females and 62% males), the mean age at study entry was 63 years (± 12 years). All cases presented with high blast counts in the BM of 65% ± 20 %. B-cell lymphoid markers were seen in 48% of the cases. The presence of lymphoid markers did not, however, meet the criteria of mixed phenotype acute leukemia. A majority of patients (90%) received intensive chemotherapy, 48% of the cases obtained first-line TKI therapy, and 33% were subjected to allogeneic stem cell transplantation in CR (Table 1 and Table S1). As expected, the seven patients that received an allogeneic stem cell transplantation exhibited a superior overall survival; the group of transplanted patients did not reach the median overall survival after a median follow up of almost 10 years (119 months), as compared to the group of non-transplanted patients that reached a median overall survival of 5 months ($P = .001$, data not shown).

3.2 | Cytogenetics and *BCR-ABL1* transcripts

Conventional G-banding of the AML cases revealed, apart from t(9;22), additional aberrations in 12 of the 21 cases (57%) with class-

TABLE 1 Characteristics of 21 acute myeloid leukemia patients with t(9;22)

Characteristic	Value ^a
Age at study entry - year	63 \pm 12
Female:male - no. (%)	8:13 (38:62)
BM blasts - %	65 \pm 20
B-cell lymphoid markers no. (%)	10 (48)
Additional chromosomal aberrations - no. (%)	12 (57)
P190/P210/unknown - no.	5/7/9
Intensive treatment - no. (%)	19 (90)
First-line TKI therapy - no. (%)	10 (48)
Allo SCT - no. (%)	7 (33)

Abbreviations: BM, bone marrow; no., number of patients; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor.

^aPlus-minus values are means \pm SD.

defining lesions in AML, such as -5 or del(5q), -7 , or $-17/abn(17p)$ in four cases.^{3,5} The *BCR-ABL1* P190/P210 isoforms were evenly distributed in the 12 cases with available data; five cases expressed the P190 fusion transcript and seven cases the P210 chimera (Table 1, Figure 1 and Table S1).

3.3 | Somatic mutations in AML with t(9;22)

Next-generation sequencing data on the 21 AML cases with t(9;22) revealed a total of 26 mutations (median 1, range 0-3) in 11 genes (Figure 1). Six genes (*RUNX1*, *IDH2*, *TP53*, *ASXL1*, *BCOR*, and *SRSF2*) were recurrently mutated (present in ≥ 2 cases). Seventeen cases (81%) harbored at least one mutation in one of the 54 genes included in the panel, whereas four patients lacked detectable mutations in this set of genes. Strikingly, eight of the 21 cases (38%) displayed mutations in *RUNX1* which are risk-stratifying in AML,⁵ and a total of nine different *RUNX1* mutations were identified in the eight cases (Figure 1). Four of the *RUNX1* mutations were missense, four were truncating and one was located in a splice region (Table S2). Of the nine mutations in *RUNX1*, seven were located in the Runt domain, suggesting a pathogenetic impact in agreement with the localization of *RUNX1* mutations in large-scale studies of AML¹⁷ (Figure 2). Six of eight (75%) *RUNX1*-mutated cases also harbored additional structural or numerical chromosomal aberrations, of which two cases presented with a trisomy 21 (Table S1). Eight of 21 cases (38%) displayed mutations in genes associated with RNA splicing (*SRSF2*, *SF3B1*) or chromatin regulation (*ASXL1*, *STAG2*, *BCOR*, *BCORL1*). Notably, mutations in these genes, similar to mutations in *RUNX1*, confer poor prognosis in several myeloid malignancies.^{5,17} Two of the eight cases that presented mutations in genes involved in chromatin regulation and RNA splicing also harbored risk-stratifying mutations in *TP53* and/or in *IDH2* p.R140.⁵ The remaining four of the 17 cases with detectable mutations exhibited mutations in either *TP53*, *IDH2* p.R172, *NRAS* or *TET2* (Figure 1, Table S2). The VAF for

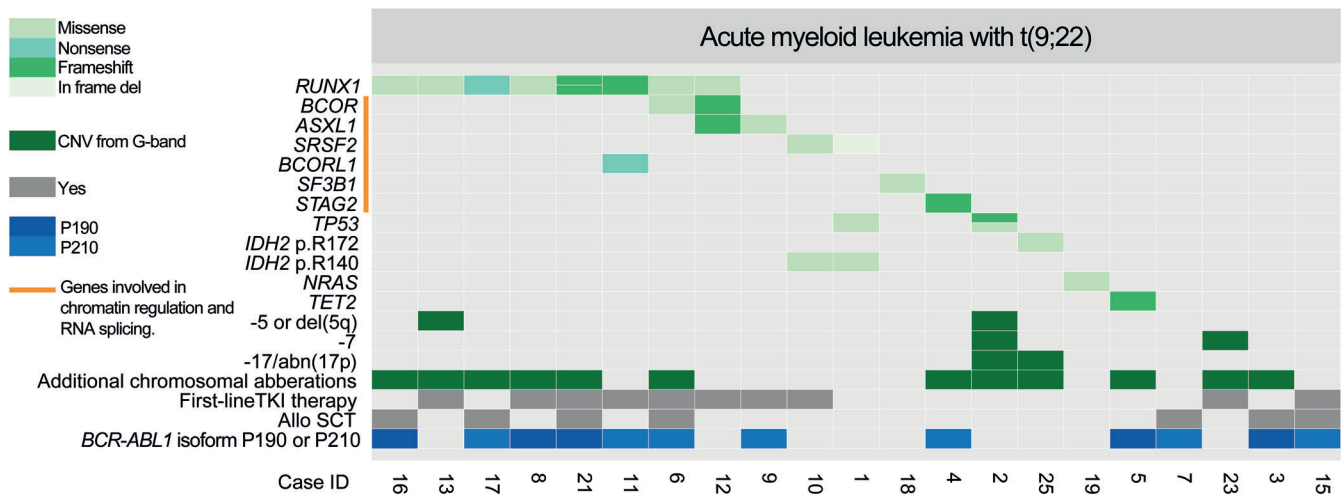


FIGURE 1 Genomic lesions and therapy in acute myeloid leukemia (AML) with t(9;22). Each row represents individual genomic lesions or option of therapy. Each column represents a single patient. Shades of green color indicate mutations or additional chromosomal aberration/–s apart from t(9;22). Dark grey color indicates whether the patient received first-line TKI therapy and/or underwent allogeneic stem cell transplantation. Shades of blue color specify type of BCR-ABL1 isoform (no color indicates lack of information). The orange line marks genes involved in chromatin regulation and RNA splicing. The patients have been listed by: RUNX1 as the gene with highest number of mutations, genes involved in chromatin regulation and RNA splicing, number of mutations and alphabetic order

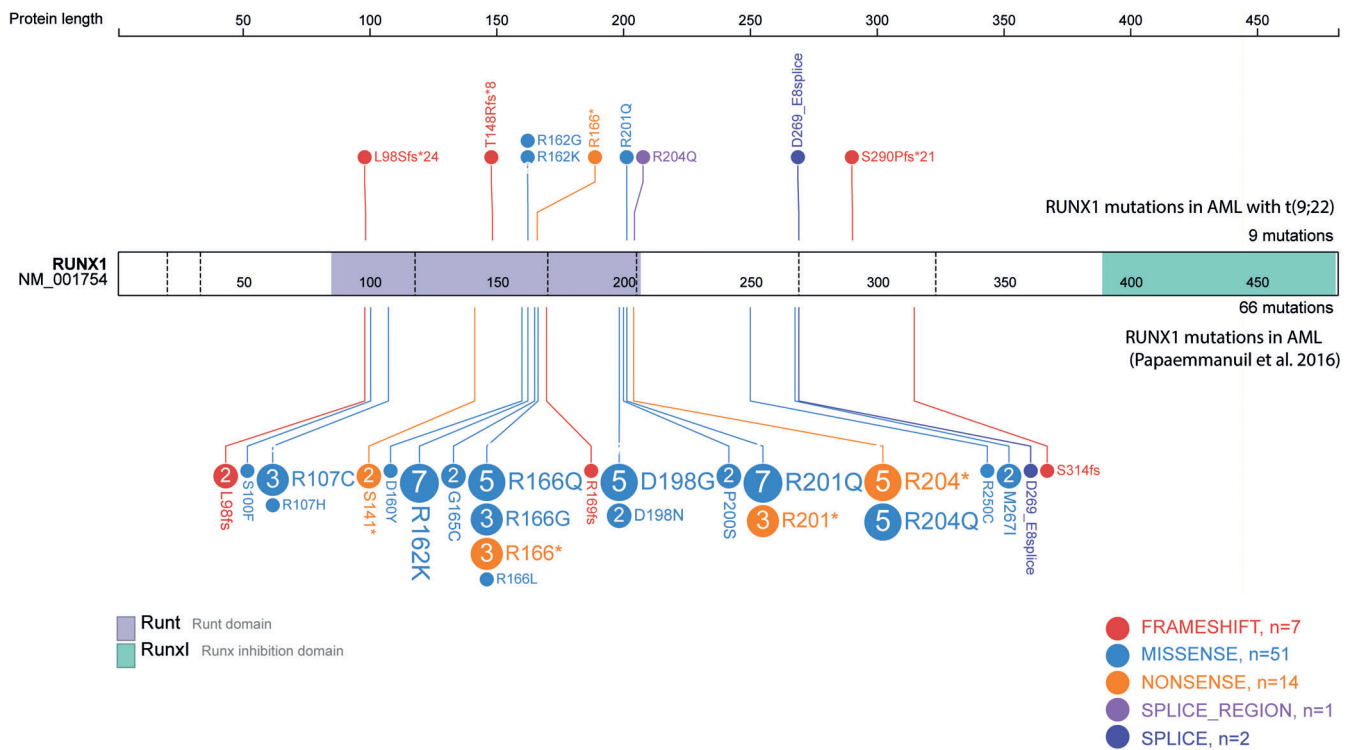


FIGURE 2 Protein paint visualizing mutations in the RUNX1 protein. Mutations above the RUNX1 protein illustrate the protein-altering mutations identified in our acute myeloid leukemia (AML) t(9;22) cohort. Mutations below the RUNX1 protein illustrate the protein-altering mutations identified in AML patients as reported in Papaemmanuil et al.¹⁶ The majority of mutations in both cohorts are localized in the Runt domain

the mutated genes ranged from 19% to 96% (median 47%), implying heterozygous or homozygous mutations in a large proportion of the cells (Table S2). Complementary PCR analysis revealed that no cases were positive for FLT3-ITD.

3.4 | Superior survival in RUNX1 mutated cases

Surprisingly, cases carrying a RUNX1 mutation (n = 8) exhibited a superior overall survival compared to wildtype cases (n = 13, P = .055,

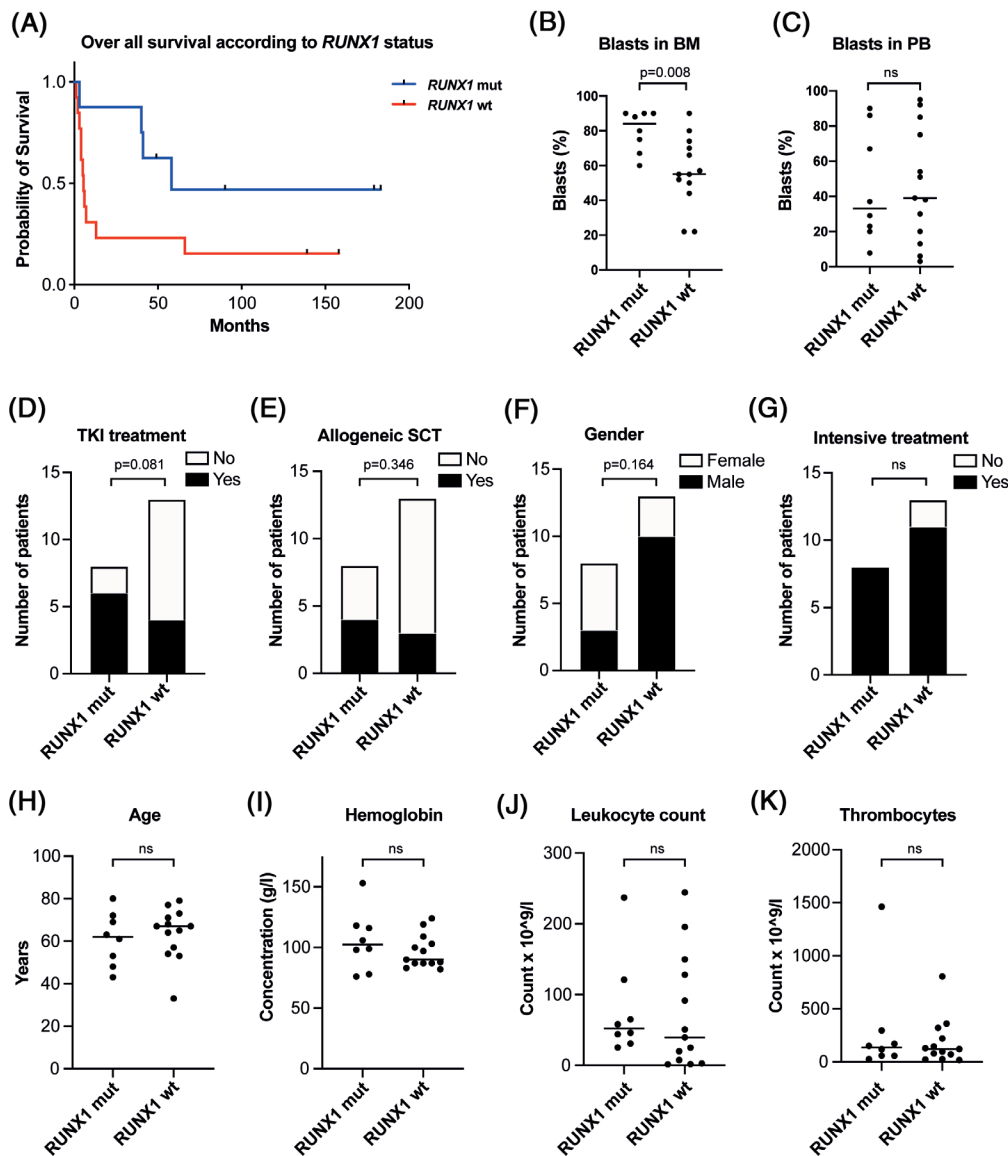


FIGURE 3 *RUNX1*-mutated cases show a favorable overall survival. (A) Kaplan-Meier survival plots showing a superior overall survival of acute myeloid leukemia (AML) patients with *RUNX1* mutations compared to wildtype cases. (B-C) Scatterplot showing a statistically significantly higher blast percent in the bone marrow of *RUNX1*-mutated cases at the time of diagnosis but not in the peripheral blood. (D-F) Barplots showing non-significant trends towards higher frequencies of TKI treatment, allogeneic stem cell transplantations and female gender in the *RUNX1*-mutated group, respectively. (G-K) Plots showing no significant difference between *RUNX1*-mutated and wildtype groups regarding frequency of intensive treatment, age at diagnosis, hemoglobin concentration, leukocyte count, or thrombocyte count, respectively

TABLE 2 Recurrently mutated genes in AML with t(9;22) and in CML in myeloid blast crisis. Mutated genes and frequency of mutations in our AML t(9;22) cohort, compared to previously published cohorts of AML patients with t(9;22) and CML-MBC

Study (number of genes investigated)	Cases (no)	<i>IDH1/DH2</i>										
		<i>RUNX1</i>	<i>ASXL1</i>	<i>BCOR</i>	<i>SRSF2</i>	<i>TP53</i>	<i>BCORL1</i>	<i>NRAS</i>	<i>SF3B1</i>	<i>STAG2</i>	<i>TET2</i>	
Present study of AML with t(9;22) (54)	AML with t(9;22) (21)	38%	14%	10%	10%	10%	10%	5%	5%	5%	5%	5%
Eisfeld et al. ²⁰ (79)	AML with t(9;22) (15)	47%	7%	20%	13%	13%	ND	7%	ND	ND	7%	ND
Grossman et al. ²² (11)	CML-MBC (24)	38%	13%	33%	N/A	N/A	4%	N/A	4%	N/A	N/A	8%
Branford et al. ²¹ (WES)	CML-MBC (19)	26%	5%	37%	5%	ND	ND	11%	ND	ND	ND	ND

Abbreviations: AML, acute myeloid leukemia; CML-MBC, chronic myeloid leukemia in myeloid blast crisis; N/A, data not available; ND, no detected mutation; no, number of patients; WES, whole exome sequencing.

Figure 3A), the difference being statistically significant when censoring patients at the time of transplantation ($P = .042$). However, the two groups were not fully comparable; the *RUNX1*-mutated group showed a higher blast count in the BM at diagnosis ($P = .008$, Figure 3B), whereas no difference was seen in peripheral blood (Figure 3C). Furthermore, the *RUNX1*-mutated group further showed non-significant trends towards a higher frequency of TKI treatment, allogeneic stem cell transplantation, and female gender (Figure 3D-F). Due to the low number of patients, multivariate analyses were not performed. However, treatment with TKI did not significantly alter the overall survival in the cohort as a whole ($P = .932$, data not shown). There were no statistically significant differences between *RUNX1*-mutated cases and wildtype cases with regard to frequency of intensive treatment, age at diagnosis, hemoglobin concentration, leukocyte or thrombocyte count (Figure 3G-K).

4 | DISCUSSION

The existence of AML with *BCR-ABL1* as a distinct disease entity has been debated, but in 2016 it was accepted by WHO as a separate, although provisional, entity.³ Aberrations such as mutations in *NPM1*, deletions of antigen receptor genes and loss of regions in *IKZF1* and *CDKN2A* have all been proposed to support a diagnosis of de novo AML disease.^{6,9} In this study, we retrospectively performed next-generation sequencing using a 54-gene panel to identify genetic markers characteristic of AML with t(9;22). Our patient cohort was selected based on strictly defined clinical criteria and is, to the best of our knowledge, the largest molecular characterization of AML with t(9;22). Among the 21 patients analyzed, we identified 26 mutations (median of one mutation per patient) in 11 genes, all previously described as recurrent driver mutations in AML.^{17,18} *RUNX1* was the most commonly mutated gene, altered in eight of 21 cases (38%) (Figure 1). Mutations were also observed in *TP53* (10%) and *ASXL1* (10%) that, similar to *RUNX1*, constitute risk-stratifying aberrations in AML.⁵ Mutations in five genes altered in this cohort (*BCOR*, *BCORL1*, *SF3B1*, *SRSF2*, and *STAG2*), together with mutations in *ASXL1* and *RUNX1*, are associated with the proposed AML high-risk-defining group chromatin-spliceosome.¹⁷ In addition, mutations were also found in *IDH2*, *NRAS*, and *TET2*. Strikingly, we did not identify any mutations among the most commonly mutated genes in AML, that is, *FLT3*, *NPM1*, or *DNMT3A* (Figure 1). Mutations in *NPM1* and *FLT3* have been reported in AML with t(9;22) previously.⁹ In that prior study, 14 genes were investigated in nine AML cases with t(9;22) and five CML in BP cases. The authors found a presence of *NPM1* mutations to be characteristic for AML with t(9;22). *NPM1* is mutated in a third of all AML patients but in our cohort no mutations were identified.^{17,18} Mutations in *NPM1* are, however, typically associated with a normal karyotype and generally considered mutually exclusive with balanced chromosomal aberrations, such as t(9;22).¹⁹ Thus, although the mutation pattern identified in this cohort is similar to previously reported large-scale studies of AML,^{17,18} we observe a distinct lack of mutations in *FLT3*, *NPM1* and *DNMT3A* and an overrepresentation of

RUNX1 mutations, observed in 38% of our cases compared to 10% reported in larger series of AML.^{17,18} In a recent study, specific mutations associated with recurrent cytogenetic aberrations in AML were investigated by a panel of 80 genes, with 15 of these cases constituting AML with t(9;22).²⁰ In line with our findings, the most commonly mutated genes were *RUNX1* (47%) and genes involved in chromatin regulation and RNA splicing (eg, *ASXL1*, *BCOR*, *SRSF2*, and *ZRSR2*) (Table 2). No mutations were found in *NPM1* or *FLT3*. However, in contrast to our findings, mutations in *DNMT3A* were observed. In addition, none of the genes *TP53*, *TET2*, and *NRAS* was found to be mutated among the 15 cases.²⁰ However, the overall findings of a high mutation rate of *RUNX1*, together with mutations in genes associated with chromatin regulation and RNA splicing, agree well with the findings in our cohort of AML with t(9;22). Significant controversy exists about whether AML with t(9;22)/*BCR-ABL1*, as suggested by WHO 2016,³ should constitute a provisional entity of AML, or if this category rather represents CML in myeloid BC with a short and/or undetectable previous chronic phase.⁷ Despite the fact that the two disease entities have different clinical characteristics, concomitant or secondary mutations to t(9;22)/*BCR-ABL1* may provide clues if they share a common molecular basis. Indeed, the mutational spectrum observed in our cohort of AML with t(9;22) to a large extent resembles other studies where genomic analyses have been performed on CML patients in myeloid BC.²¹⁻²³ Two separate studies, including 24 and 19 cases of CML in myeloid BC, respectively, used a 9-gene panel or whole exome sequencing (WES) to identify additional mutations. A majority of the mutations were identified in *RUNX1* (38% and 26%) and *ASXL1* (33% and 37%, respectively) together with mutations in other chromatin and spliceosome-genes (eg, *BCORL1*, *BCOR*, *PHF6*, and *U2AF1*) as well as in *IDH1/2*, *NRAS*, *TET2*, and *TP53* (Table 2). Thus, the high prevalence of mutations in *RUNX1* and lack of mutations in *NPM1* and *FLT3*, as seen in our cohort, does not seem to represent a distinct feature of AML with t(9;22), but rather agrees well with the mutational pattern observed in CML in myeloid BC.^{20-22,24} The *RUNX1* gene product is a well-characterized transcription factor that is essential for normal hematopoiesis and a master regulator of hematopoietic differentiation.²⁵ Somatic mutations in *RUNX1* are common in myeloid leukemias and are risk-stratifying in AML.^{5,17,18} Most *RUNX1* mutations in AML are missense or truncating, affecting the conserved DNA-binding Runt domain (Figure 2).¹⁷ Recurrent mutations in *RUNX1* have also been reported in multiple studies of CML in BC and, as in AML, the majority of the identified mutations reside in the Runt domain.^{21,23,26-28} In line with this, seven of the nine *RUNX1* mutations in this study occurred in the Runt domain (Figure 2). Thus, despite the frequent occurrence of *RUNX1*-mutated cases in our study, we do not see a distinct pattern for the *RUNX1* mutations distinguishing t(9;22)-positive AML from *RUNX1*-mutated CML in BC in general. Mutations in *RUNX1* are associated with a poor prognosis in AML.⁵ However, survival data on *RUNX1*-mutated cases in our cohort unexpectedly showed a significantly prolonged overall survival (Figure 3A), although our study cohort was too small to establish conclusively survival differences. Conceivably, the better prognosis for *RUNX1*-positive cases in our cohort could be due to

overrepresentation of TKI-treatment or allogeneic stem cell transplantations in the *RUNX1*-positive group, although the differences between the groups were not statistically significant (Figure 3D,E). Thus, the prognostic importance of *RUNX1* mutations in AML with t(9;22), as in CML in myeloid BC,²¹ remains to be established in future larger studies. CML in lymphoid BC commonly harbors whole gene or exon deletions targeting *IKZF1*.^{20,21} *IKZF1* deletions have previously been reported as recurrent findings in AML with *BCR-ABL1*, together with cryptic deletions within the immunoglobulin and T cell receptor genes.⁶ Our amplicon-based gene panel analysis does not cover large structural variants (whole genes or exons), and due to lack of sufficient material we could not proceed with analysis detecting larger structural aberrations (eg, single nucleotide polymorphism array, whole exome sequencing or whole genome sequencing) in *IKZF1* and *CDKN2A*. Conventional G-banding revealed additional chromosomal aberrations in 57% cases, which is slightly higher than the 33% previously described in cases defined as AML with *BCR-ABL*, but in line with the 60% to 80% described in CML in BC.^{7,9,29} In conclusion, we here describe the clinical findings and molecular characteristics of AML with t(9;22) in a retrospective population-based study, representing the largest cohort of this disease entity available to date. Based on the molecular characteristics, our results do not support a distinction between CML in myeloid BC and the provisional entity AML with t(9;22)/*BCR-ABL1* as defined by the WHO 2016 classification.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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