RESEARCH LETTER

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TO THE EDITOR:

Characterization of cases with the rare cytogenetic abnormality i(7)(p10) reveals an association with IDH2-mutated AML

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Chromosomal aberrations play a pivotal role in hematological neoplasms, and their identification has profound clinical implications. In many hematological malignancies, including acute myeloid leukemia (AML), the identification of recurrent genetic alterations is critical for the classification and prognostication according to the World Health Organization (WHO) and European LeukemiaNet guidelines.[1,2] The isochromosome of the short arm of chromosome 7, i(7)(p10), represents a chromosomal alteration leading to the loss of the long arm (7q) and a duplication of the short arm (7p). To date, there has been only limited systematic analysis of the presence, frequency, and clinical implications of i(7)(p10) in hematological neoplasms; although recently, a patient diagnosed with AML and i(7)(p10) as sole chromosomal abnormality was described and characterized.[3] In the 2022 WHO classification, a clear distinction is made between "AML, defined by differentiation" and "AML with defining genetic abnormalities." The latter category encompasses the subtype AML with myelodysplasia-related (MR) changes with various defining cytogenetic abnormalities including monosomy 7, 7q deletion or loss of 7q due to unbalanced translocation.[1] Thus, AML with i(7)(p10) is formally grouped into the AML-MR subgroup.[3]

In addition to the aforementioned patient case, the Mitelman Database of Chromosome Aberrations and Gene Fusions in Cancer describes 7 other AML cases with i(7)(p10) as a sole chromosomal alteration, bringing the total number of reported cases, to our knowledge, to only 8.[4] Our study aims to address this knowledge gap by systematically analyzing the frequency and occurrence of i(7)(p10) in hematological malignancies, further characterizing additional cytogenetic alterations, identify co-occuring mutations and examine potential clinical implications associated with i(7)(p10).

Diagnoses (from peripheral blood and/or bone marrow) were established based on cytomorphology, immunophenotype, cytogenetics and molecular genetics as previously published according to respective WHO classifications.[1,5,6] All patients had given written informed consent to the use of genetic and clinical data according to the Declaration of Helsinki. The study was approved by our internal institutional review board. Cytogenetic and molecular genetic analyses were performed as previously described according to standard methods.[7,8] SPSS (version 19.0.0) software (IBM Corporation, Armonk, NY) was used for statistical analyses. All reported P values are 2-sided and were considered significant at $P \leq .05$.

Our systematic analysis of 197 467 cases send to MLL Munich Leukemia Laboratory for chromosome banding analysis between September 2005 and June 2022 revealed i(7)(p10) in 34 cases within our patient database. A striking 68% of the identified cases (23/34) were detected in patients diagnosed with AML, making this the most common entity associated with i(7)(p10). Other hematological neoplasms were diagnosed less frequently including mature B-cell neoplasms (B-NHL) in 18% of cases (6/34), myelodysplastic neoplasms in 12% (4/34), and acute lymphoblastic leukemia in 3% of cases (1/34, Figure 1A). Interestingly, i(7)(p10) was found as the sole cytogenetic abnormality in 20 of 34 cases. Almost all of these patients were diagnosed with AML (19 cases), besides 1 case of myelodysplastic neoplasms. Of the remaining cases, 10 cases exhibited additional chromosomal alterations, resulting in a complex karyotype in 5 of 10 cases. Notably, all cases with a complex karyotype were

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The full-text version of this article contains a data supplement.

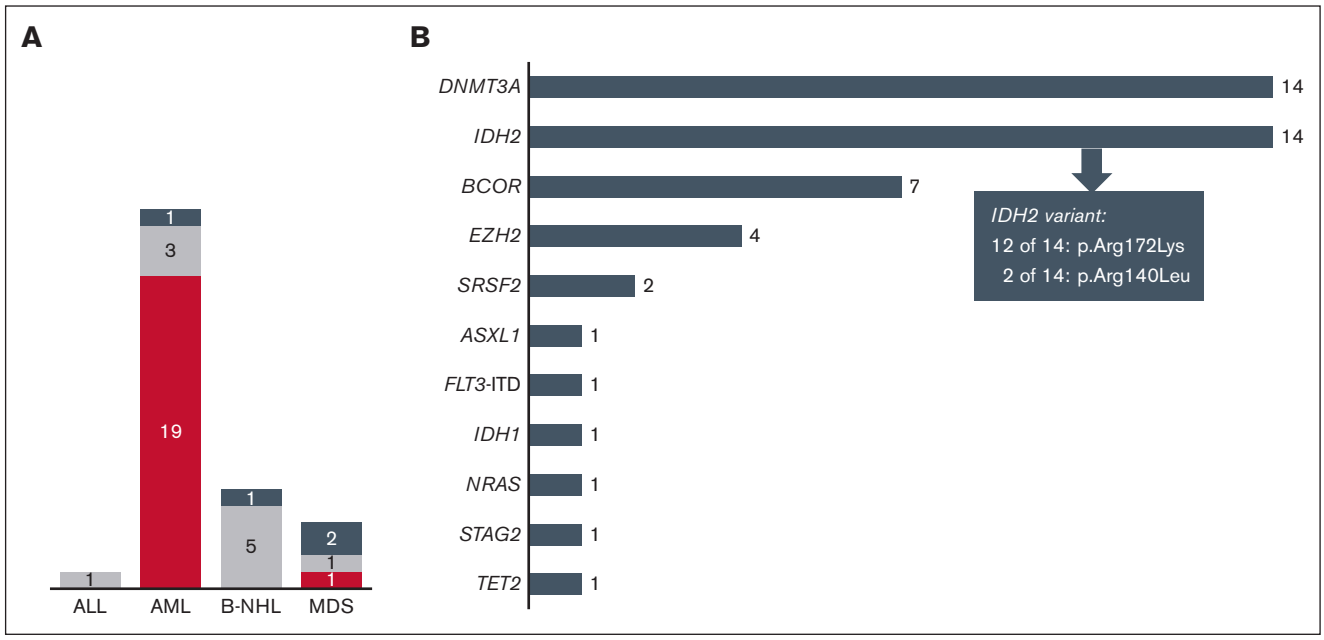

Figure 1. Summary of co-occurring cytogenetic alterations and comutations. (A) Occurrence of i(7)(p10) and other cytogenetic alterations. The number of cases in which i(7)(p10) was detected in the respective entities is depicted. The color indicates the presence of other cytogenetic alterations (light gray), the detection of i(7)(p10) in a subclone only (dark gray) or the presence as sole abnormality (red). (B) Number of cases with the respective comutations among the 15 AML cases with i(7)(p10). For *IDH2* the mutation site is also depicted.

diagnosed as mature B-cell neoplasms (B-NHL). In 4 cases, i(7)(p10) was found in a subclone. Molecular genetic data were available for 18 of 34 cases, offering insights into the genetic landscape of i(7)(p10)–associated hematological neoplasms. Among these cases, *DNMT3A* (15/18), *IDH2* (14/18), and *BCOR* (7/18) were revealed as the most frequently mutated genes. Because these 18 cases comprised 15 cases diagnosed with AML, further analysis focused on these patients only. Of the 15 cases, mutations in *DNMT3A* and *IDH2* were detected in 14 cases, and *BCOR* and *EZH2* mutations were detected in 7 and 4 cases, respectively (Figure 1B). Of note, in the remaining patient (n = 1) of our cohort not harboring an *IDH2* mutation, an *IDH1* mutation was detected. Interestingly, the observed pattern of co-occurring mutations in our study differed from the patterns typically associated with AML featuring *IDH2* mutations: mutations in *SRSF2*, *ASXL1*, *NPM1, FLT3*-ITD, *RUNX1*, and *NRAS*,[9,10] were absent or only rarely detected in cases with i(7)(p10) (Figure 1B).

For *IDH2* mutations, typical hot spots are known, in which almost all mutations are located, mainly comprising the sites Arg140 and Arg172.[10-12] Within our subset of cases harboring *IDH2* mutations, the p.Arg172Lys mutation site dominated in 12 out of 14 (86%) cases. In contrast, p.Arg140Leu, the usually more common *IDH2* mutation site, was present in 2 of 14 (14%) cases only. We compared this prevalence of p.Arg172Lys with a control cohort of 60 cases of AML with *IDH2* mutation but without i(7)(p10). In fact, only 8 out of 60 (13%) cases with p.Arg172Lys were detected, the majority (52/60, 87%) included the p.Arg140Leu mutation site (86% vs 13%; $P < .001$). Of note, only 1 of the 60 cases of *IDH2*-mutated AML without i(7)(p10), showed a monosomy 7 or a del(7q) due to an unbalanced translocation. None of the cases had del(7q) as an isolated abnormality, which underlines the specific association of *IDH2* mutation with i(7)(p10). Analysis of the variant allele frequency (VAF) of *IDH2* mutations compared with the VAF of comutations revealed that *IDH2* was always present in the main clone, although the median *IDH2* VAF in AML cases with i(7)(p10) was slightly lower than in AML cases without i(7)(p10) (38.3% vs 45.9%, not statistically significant). We further assessed clinical attributes of *IDH2*–mutated AML cases with and without i(7)(p10). This revealed a predominance of females (13/14, 93% vs 29/60, 48%; $P < .001$) and patients were notably younger than their counterparts without i(7)(p10), with an average age of 63 years compared with 72 years ($P = .015$). Further, the white blood count was found to be significantly lower (median $2.2*10^3$ µL vs $8.8*10^3$ µL; $P < .001$) while no differences were detected regarding blast count and other blood parameters (supplemental Table 1). The analysis of the overall survival did not reveal a statistically significant difference between patients with i(7)(p10) and those with *IDH2*-mutated AML without i(7)(p10) (37 months vs 14 months; $P = .402$).

Our patient cohort clearly demonstrates a predominant association of i(7)(p10) with *IDH1/2* mutated AML. Of special interest is the presence of i(7)(p10) as a sole abnormality in the vast majority of AML cases, suggesting a role of i(7)(p10) in pathogenesis of this AML subtype. AML with i(7)(p10) meets formal definition of the WHO–defined AML-MR subtype ,[1] and a recent report concluded that i(7)(p10) should be grouped within this specific category.[3] This previously described patient case also harbored an *IDH2* mutation in addition to i(7)(p10), which was similar to 14 of our 15 cases.[3] *IDH* mutations are of special clinical interest since they are the target of inhibitors, such as ivosidenib (*IDH1*) and enasidenib (*IDH2*), both Food and Drug Administration (FDA)-approved for AML-treatment with *IDH* mutations.[13-15] Because *IDH2* mutations

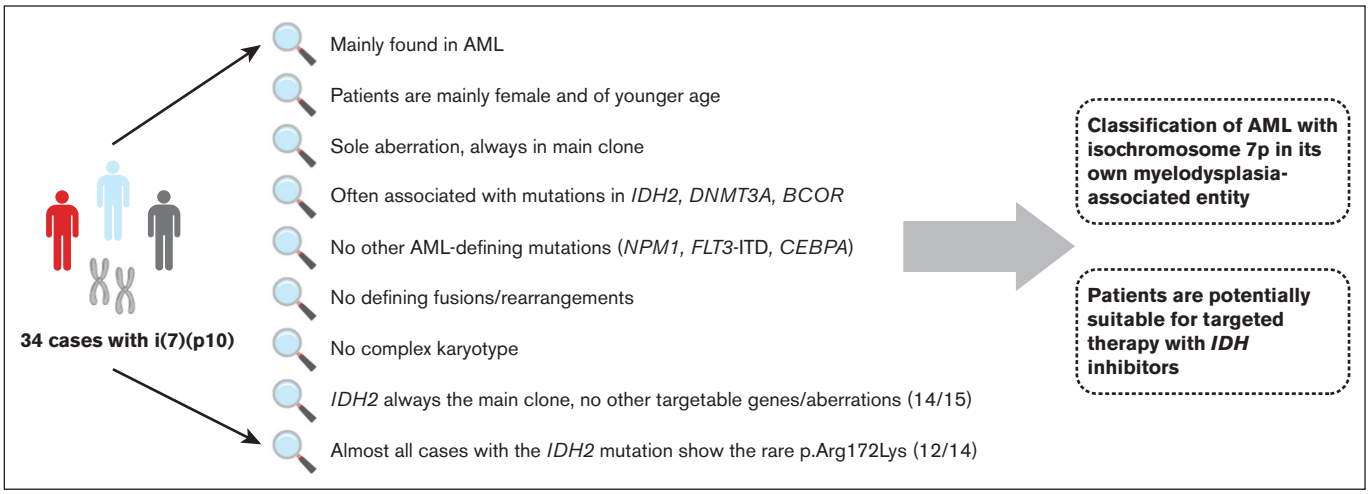

Figure 2. Summary of characteristic features of cases with the cytogenetic abnormality i(7)(p10). Graphical summary of genetic and clinical features observed for the 34 patients with i(7)(p10).

in our patient cohort were always detected in the main clone, these patients are potentially suitable for targeted therapy. Interestingly, a previous report characterizing myeloid malignancies with isolated 7q deletion revealed a high frequency of mutations in *ASXL1, TET2, RUNX1* and *SRSF2* which were very infrequent or even completely absent in the i(7)(p10) cohort, further distinguishing cases with i(7)(p10) from other cases with 7q loss.[16] This is also underlined by differences in sex predominance (females 37% vs 93%) and age (72 vs 63 years) in the del(7q) and i(7)(p10) cohort.[16]

Although the numbers of patients are still small, to our knowledge, here we characterized the largest cohort by far with this rare cytogenetic alteration and provide clear evidence that the analyzed patient cohort stands out as a distinct group with defining characteristics (Figure 2; supplemental Table 2), including (1) the single aberration i(7)(p10) as most characteristic feature, (2) the frequency of *IDH2* mutations at the rather rare site p.Arg172Lys, (3) the predominance of females and (4) younger age of patients that are affected by *IDH2*-mutated AML with i(7)(p10). Additionally, the association with *IDH2/1* mutations and the lack of other AML defining alterations offers therapeutic strategies (targeted therapy with *IDH* inhibitors) for patients with this rare cytogenetic alteration. These characteristics as well as low frequencies of mutations defining AML-MR suggest that one should be cautious with classifying AML cases with i(7)(p10) as AML-MR. Understanding the functional consequences of i(7)(p10) and its effects on hematological malignancies will be a next step in elucidating the biology of this chromosomal abnormality.

The study has been approved by the internal review board of the MLL Munich Leukemia Laboratory. This study contains only laboratory data from a large cohort of patients. No clinical trial was performed.

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Contribution: A.S. and C.H. designed the study; A.S. interpreted the data; A.S., C.K., and K.H. wrote the manuscript; A.S. and C.H. were responsible for chromosome banding and fluorescence in situ hybridization analyses; M.M. was responsible for molecular and bioinformatic analyses; W.K. was responsible for immunophenotyping; T.H. was responsible for cytomorphologic analyses; and all authors read and contributed to the final version of the manuscript.

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