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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

AML with t(4;12)(q12;p13): A Detailed Genomic and Transcriptomic Analysis Reveals Genomic Breakpoint Heterogeneity, Absence of *Pdgfra* Fusion Transcripts and Presence of *Pdgfra* Overexpression in a Subset of Cases

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Background: Gene fusions are a frequent event in acute myeloid leukaemia (AML). It is estimated that about 40% of AML patients harbour a cytogenetic abnormality resulting in a gene fusion. However, AML with t(4;12)(q12;p13) is very rare, but it is often accompanied by an aggressive clinical course and a poor prognosis. As frequently indicated by fluorescence in situ hybridization analyses (FISH), patients are assumed to harbor an *ETV6::PDGFRA* fusion, which impacts the choice of therapy, as these patients can be treated with tyrosine kinase inhibitors. The genomic region on chromosome 4 involved in *ETV6* rearrangements is densly packed with genes in close spatial proximity. Therefore, the resolution of chromosome banding analysis and also FISH is not sufficient to fully elucidate the fusion partners involved. Recent studies have pointed out that many of these patients do not harbor an *ETV6::PDGFRA* fusion but other rather unknown fusion partners have been elucidated.
Aim: (1) Evaluation of the genomic breakpoints in patients with t(4;12)(q12;p13) *ETV6*-rearranged AML; (2) determine the alteration of *PDGFRA* expression in patients with t(4;12).
Patients and Methods: 10 patients (F: 4, M: 6; median age: 63 [44-82] years) with a t(4;12)(q12;p13) indicated by FISH and chromosome analysis were included. Samples were analysed by whole genome and whole transcriptome sequencing (WGS/WTS). Sequencing was performed on NovaSeq instrument (Illumina). Fusions were called with Arriba, STAR-Fusion and Manta. For gene expression analysis WTS data were log2 transformed and normalized with the trimmed mean of M-values (TMM) method.
Results: Based on chromosome analysis and FISH patients showed break events in 4q12 and 12p13. In all cases a FISH signal constellation typical for an *ETV6* rearrangement was observed.
The mutation spectrum for each patient of the most commonly mutated genes in AML was examined by use of WGS data. The median number of mutations was 3, with mutations in *ASXL1* being the most common (6 patients) and none of the patients featuring mutations in the *PDGFRA* gene.
WTS analysis revealed in-frame fusions in 6 of 10 patients involving genes located on chromosomes 4 and 12 (4 patients with *ETV6::CHIC2*, 1 patients with *ETV6::SCFD2*, 1 patient with *ETV6::ADAMTS3*). None of the 10 examined patients showed a gene fusion, or a fusion transcript involving *PDGFRA*.
Based on WTS data, 7 of the 10 patients showed a *PDGFRA* overexpression. WGS breakpoint analysis showed that genetic breakpoints on chromosome 12 cluster in introns 1 (4 patients) and 2 (6 patients) of the *ETV6* gene. In contrast chromosome breaks on chromosome 4 are heterogeneously distributed in the 4q12 region. Breakpoint comparison indicated that patients with chromosome breaks in a range from chr4:54,804,230-54,962,206 (7 patients) display *PDGFRA* overexpression. In contrast patients with chromosome breaks further downstream chr4:55,021,511-73,409,362 (3 patients) did not exhibit an increased *PDGFRA* expression. This suggests an ectopic expression of *PDGFRA* triggered by the translocation and independent of the existence of an in-frame fusion transcript. A chromosome break in the range of chr4:54,804,230-54,962,206 (seen in 7 patients) might result in the inactivation of a CTCF binding site (chr4:54,796,345-54,796,360) upstream of these chromosome breaks that is already known to induce *PDGFRA* overexpression when disrupted.
Conclusions: Analysis of AML with t(4;12)(q12;p13) translocation by WGS and WTS provides detailed information that separates two subsets distinguished by distinct breakpoint cluster regions on 4q12 and *PDGFRA* gene expression. The clinical impact of increased *PDGFRA* gene expression on response to TKI and prognosis as well as the presence of additional fusion transcripts has to be evaluated in further studies.

Disclosures Müller-Jochim: *MLL Munich Leukemia Laboratory:* Current Employment. **Meggendorfer:** *MLL Munich Leukemia Laboratory:* Current Employment. **Walter:** *MLL Munich Leukemia Laboratory:* Current Employment. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Kern:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership. **Haferlach:** *MLL Munich Leukemia Laboratory:* Current Employment, Other: Equity Ownership.

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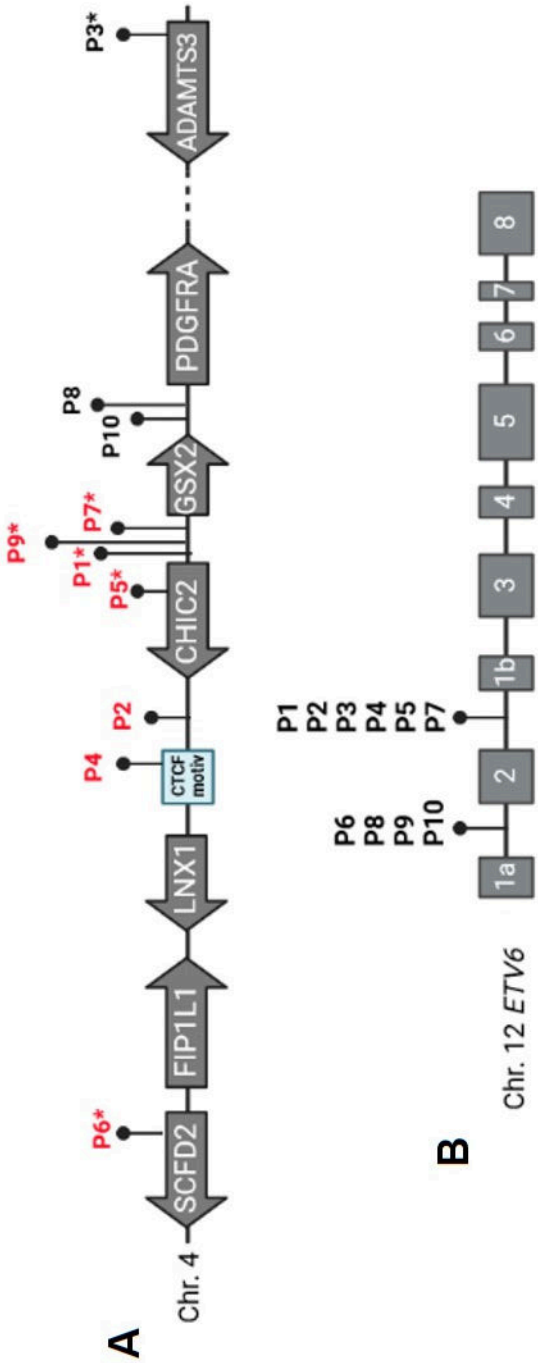

Figure 1. Schematic illustration of the genetic break points in 10 AML patients (P1-10) with t(4;12). Shown are the genetic locus 4q12 (A) and exons and introns of *ETV6* on chromosome 12 (B). (*) indicate detected in-frame fusions in these patients. Red colored lettering indicates *PDGFRA* overexpression detected in these patients. (created with BioRender.com)

Figure 1