

Leukaemia Section

Short Communication

t(7;12)(q36;p13) MNX1/ETV6

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Abstract

Review on t(7;12)(q36;p13), with data on clinics, and the genes involved.

Keywords

Chromosome 7; chromosome 12; acute myeloid leukemia.

Clinics and pathology

Disease

Phenotype/cell stem origin

Almost exclusively present in acute myeloid leukemia (AML) of various subtypes: 13 AML not specified cases (Hagemeijer et al., 1979; Wlodarska et al., 1998; Tosi et al., 2000; Slater et al., 2001; Simmons et al., 2002; Tosi et al., 2003; Ballabio et al., 2009; Wildenhain et al., 2010), 8 M0 (Tosi et al., 2000; Tosi et al., 2003; von Bergh et al., 2006; Ballabio et al., 2009; Park et al., 2009; Wildenhain et al., 2010), 2 M1 (Tosi et al., 2000; Slater et al., 2001), 7 M2 (Raimondi et al., 1999; Satake et al., 1999; von Bergh et al., 2006; Hauer et al., 2008), 1 M3 (Slater et al., 2001; Wildenhain et al., 2010), 3 M4 (Hagemeijer et al., 1981; Tosi et al., 2000; Naiel et al., 2013), 3 M5 (Tosi et al., 1998; Park et al., 2009; von Bergh et al., 2006), 1 M6 (Satake et al., 1999) and 2 M7 (Taketani et al., 2008; Naiel et al., 2013). Four cases of acute lymphoblastic leukemia (ALL) (Andreasson et al., 2000; Tosi et al., 2000; von Bergh et al., 2006) as well as 2 acute biphenotypic leukaemia patients were reported (Park et al., 2009;

Naiel et al., 2013) (Data from Naiel et al., 2013). The case that was reported previously as myelodysplastic syndrome (Tosi et al., 1998), revealed a revised diagnosis as AML (Ballabio et al., 2009).

Epidemiology

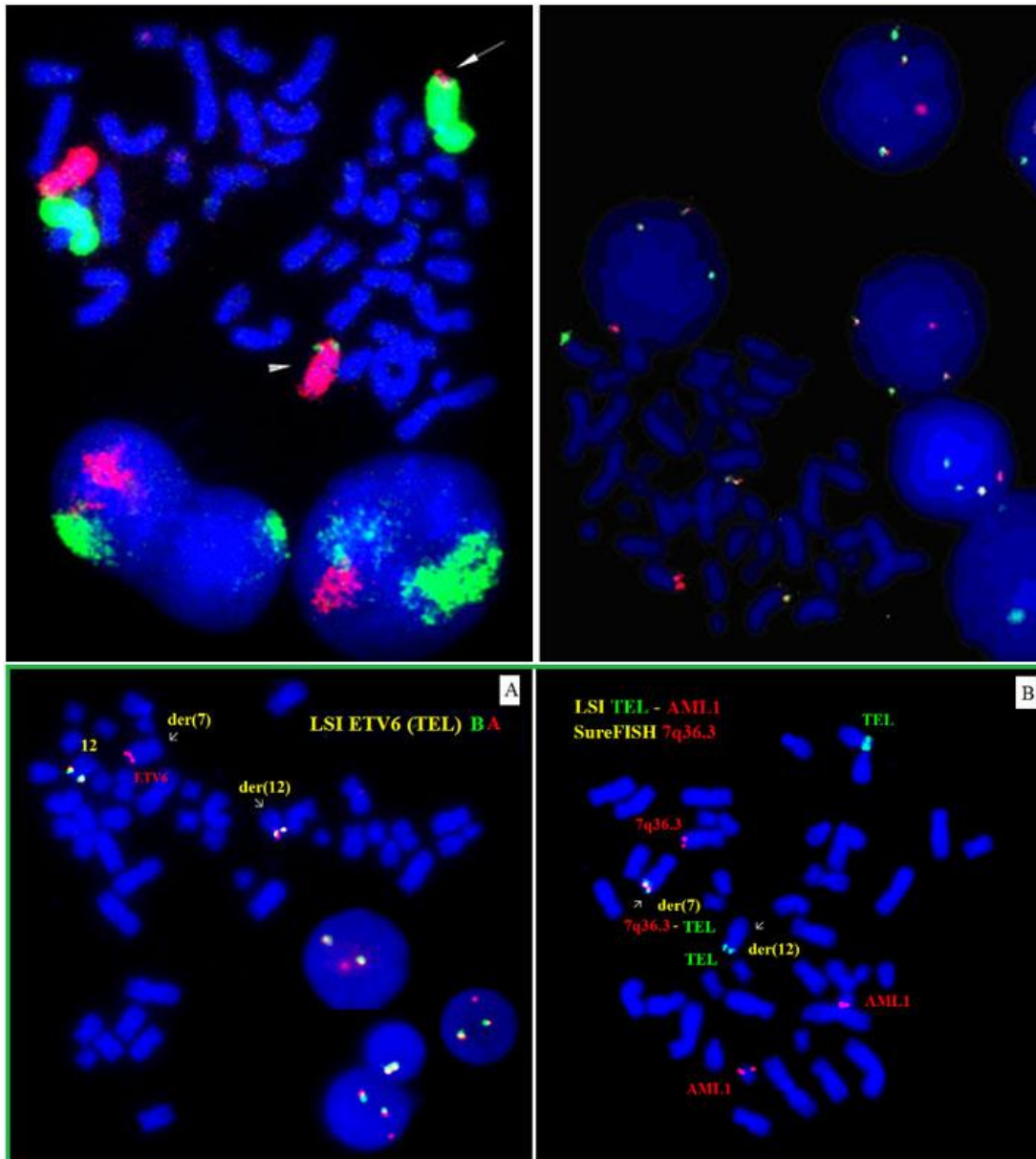
At least 47 reported cases with chromosomal translocation and/or the fusion transcript (sex ratio 19M/28F; the incidence is low (3%) in overall paediatric AML, but significant in infant AML (Neil et al., 2013; Tosi et al., 2015); extremely rare in infant ALL and older children. The translocation may be overlooked, and therefore underestimated; the estimated incidence of this translocation is approximately one third of AML paediatric patients with age between 0-2 years (von Bergh et al., 2006; Tosi et al., 2015).

Clinics

WBC range 8-230 x 10⁹/L, median 12 x 10⁹/L; organomegaly, central nervous system involvement in 7 of 12 cases (Tosi et al., 2015).

Prognosis

Inferior outcome with the standard induction therapy with probabilities of 3 years event free survival of 0-14 % and overall survival of 0-28 % (von Berg et al., 2006; Tosi et al., 2015). From the recently published data on the clinical outcome: only 5 patients are alive (1 after 22 months post BMT (Slater et al., 2001); 1 relapsed twice, but alive after 2 years after BMT (Simons et al., 2002); 1 after chemotherapy and 1 after BMT.



Top Left: example of FISH performed on bone marrow metaphase from a patient with t(7;12)(q36;p13). Dual colour FISH using whole chromosome paint specific for chromosome 7 (in green) and chromosome 12 (in red) shows the reciprocal translocation. The arrow indicates the der(7) and the arrowhead indicates the der(12) - Sabrina Tosi; **Right:** Example of double colour FISH performed on bone marrow metaphase from a patient with t(7;12)(q36;p13). The PAC clone 1121A15 for the breakpoint region at chromosome band 7q36 (in green) and a cosmid cocktail for ETV6 at chromosome band 12p13 (in red) show one green signal for the normal chromosome 7, one red signal for the normal chromosome 12 and two fusion signals at both the derivative chromosomes 7 and 12 - Anne RM von Bergh and H. Berna Beverloo.

Bottom FISH using commercially available LSI TEL (12p13) Break-apart (Vysis, Abbott, USA) probe showing juxtaposition of telomeric sequences (split red signal) to der(7) chromosome and a 2 fusion (one of them smaller appearing), 1 red signal pattern on interphase cells (A). The juxtaposition of disrupted TEL sequences to 7q36.3 may be visualized by Vysis LSI ETV6 (TEL)/RUNX1 (AML1) dual color translocation probe and SureFISH 7q36.3SHH probe (red signal) (Agilent Technologies, US) revealing the fusion signal on der(7) chromosome and the remaining TEL sequences (green) on der(12) chromosome (visualisation of 7q36.3 on derivative chromosome 12 might be impaired due to the small size of the translocated fragments) (B).

To screen for t(7;12)(q36;p13) in infants with MLL-negative AML, commercially available Vysis LSI ETV6 (TEL) break-apart probe can be used to confirm the breakage of the ETV6 gene on 12p13, showing the split signal on der(7) chromosome and the truncated fusion signal on der(12) (Figure 1A). Visualization of 7q36.3 sequences may be done by SureFISH 7q36.3SHH probe (Agilent Technologies, US) alone or with combination of Vysis LSI ETV6 (TEL)/RUNX1 (AML1) dual color translocation probe (Figure 1B) - Adriana Zamecnikova, Soad Al Bahar.

It appears to be that the only long time survival is a paediatric patient with acute megakaryocytic

leukaemia alive after 5 years, treated with chemotherapy (Taketani et al., 2008). The remaining

18 patients died during induction chemotherapy, infection or relapse (Data from Tosi et al., 2015).

Cytogenetics morphological

Not always visible by chromosome banding techniques alone; may also be misdiagnosed as del(12)(p13) and/or del(7q), thus fluorescence in situ hybridization (FISH) analysis has to be done for its identification.

Cytogenetics

Additional anomalies

Accompanied by the presence of an extra chromosome in the majority of cases: +19 mostly, occurring in 38 out of 47 cases (+19 alone in 22 cases, in association with +8 in 8, +13 in 2, +22 in 3 and with +X,+8 in 3), while +8 as a sole numerical anomaly was found in 2 patients (Data from Naiel et al., 2013).

Variants

To date, three-way complex translocations were found in 3 patients, characterized as: t(5;7;12)(q31;q36;p13), t(1;7;12)(q25;q36;p13) (Park et al., 2009) and t(7;12;16)(q36;p13;q12) (Naiel et al., 2013).

Genes involved and proteins

MNX1 (homeo box HB9)

Location

7q36.3

Note

HLXB9 mutation are found in patients with Currarino syndrome

DNA/RNA

3 exons, 2061 bp mRNA

Protein

403 AA; Homeobox protein HB9; Highly expressed in CD34+ bone marrow cells; Possibly involved in the regulation of growth and differentiation of progenitor cells.

ETV6 (ets variant 6)

Location

12p13.2

DNA/RNA

9 exons; alternate splicing

Protein

contains a Helix-Loop-Helix and ETS DNA binding domains; wide expression; nuclear localisation; ETS-related transcription factor

Cytogenetics molecular

Detectable by dual colour FISH. A cosmid cocktail or YAC 964c10 shows a split signal on the der(12) and der(7). Also the commercial probe LSI TEL/AML1 (ES) for the detection of the t(12;21) shows a split signal on the der(7) and the der(12) in the t(7;12) cases since the breakpoint in these cases falls within the first three exons, which are contained in this probe. FISH using the PAC clone RP5-1121A15 mapping to 7q36 shows a split signal on the der(7) and der(12).

Result of the chromosomal anomaly

Hybrid gene

Description

5' HLXB9 - 3' ETV6. The breakpoints on chromosome 12 disrupting the ETV6 gene are consistently at the 5' end of ETV6, between exons 1 and 3, however chromosome 7 breakpoints are scattered in regions proximal to the HLXB9 (Homeobox HB9, MNX1) gene, suggesting that HLXB9 gene is translocated to the der(12) without its disruption (Tosi et al., 2015).

Fusion protein

Note

The t(7;12) is heterogeneous at the molecular level. The presence of an HLXB9/ETV6 fusion transcript has been identified only in approximately 50 % of described patients (Beverloo et al., 2001; Simmons et al., 2002; Von Bergh et al., 2006; Taketani et al., 2008; Ballabio et al., 2009; Wildenhain et al., 2010).

Description

N-terminal HLXB9, including its polyalanine repeat region, is fused to a large C-terminal part of the ETV6 protein including its HLH domain and ETS domain; the homeobox domain of HLXB9 is not retained in the fusion protein; the reciprocal transcript is not expressed.

Oncogenesis

The pathogenic mechanisms arising from t(7;12)(q36;p13) are not fully understood. As the presence of an HLXB9/ETV6 fusion transcript has been shown only in approximately 50% of patients and the reciprocal ETV6/HLXB9 transcript has never been observed, it is unclear if generation of a fusion gene is involved in leukemogenesis, at least in some cases. In addition, the presence of a HLXB9/ETV6 protein has not been confirmed to date, thus the production of a fusion protein is still debatable (Tosi et al., 2015). While the role of a chimeric protein as an oncogenic trigger is unclear, the observation of highly increased HLXB9 expression in t(7;12)-positive patients suggests that ectopic expression of HLXB9 might promote

oncogenesis (Von Bergh et al., 2006; Ballabio et al., 2009). Alternatively, it is possible that ETV6 is the only contributor to leukaemogenesis and its disruption alone might activate oncogenesis. Furthermore, as the t(7;12) has been found associated with deletions of 12p and/or a gene(s) at 7q36, it is likely that inactivation of ETV6 and/or a gene(s) at 7q36 might contribute to the malignant phenotype (Neiel., et al. 2013).

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