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Leukaemia Section
Short Communication

t(9;12)(q34;p13) ETV6/ABL1

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Abstract

Review on t(9;12)(q34;p13) ETV6/ABL1, with data on clinics, and the genes implicated.

Clinics and pathology

Disease

Malignant hemopathies (26 cases reported)

Phenotype/cell stem origin

AML (3 cases), B-cell ALL (8 cases), T-cell ALL (1 case), RAEB evolving into AML (1 case), chronic myeloproliferative neoplasm (2 cases), Philadelphia chromosome-negative CML (11 cases).

Epidemiology

Gender: 17 males, 8 females; age at diagnosis: 8 months to 81 years.

Clinics

Eosinophilia appears to be a common feature of malignancies associated with the ETV6-ABL1 fusion gene (15/20 cases).

Genetics

Note

The t(9;12)(q34;p13) involves the ETV6 gene (12p13), a transcription factor frequently rearranged in myeloid and lymphoid leukemias. More than 30 ETV6 fusion gene partners have been described. Most translocations involving ETV6 generate fusion genes that lead to the activation of transcription factors or kinases but other mechanisms are also known (loss of function of the fusion gene affecting ETV6 and the partner gene, activation of a proto-oncogene in the vicinity of a chromosomal translocation and dominant negative effect of the fusion protein over transcriptional repression mediated by wild-type ETV6).

Cytogenetics

Note

t(9;12)(q34;p13) as the sole abnormality or associated with other abnormalities.

Cytogenetics morphological

t(9;12)(q34;p13) is very difficult to be identified by conventional cytogenetics.

Cytogenetics molecular

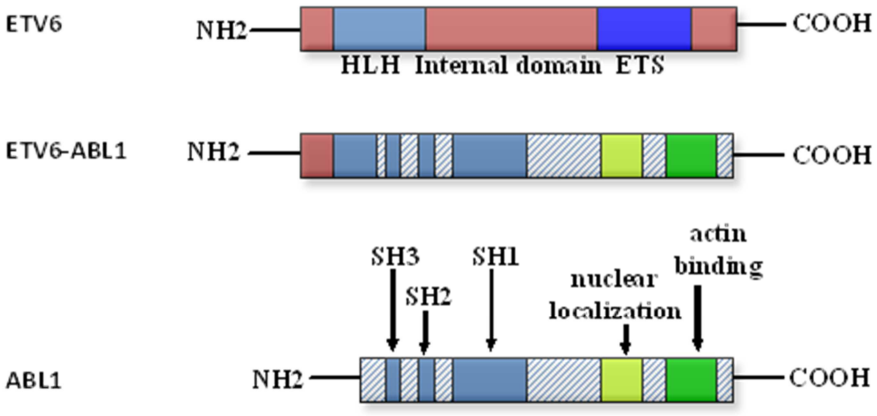
t(9;12)(q34;p13) usually requires FISH analysis with ETV6 and ABL1 probes to be detected (cryptic translocation). Insertions are also frequently identified.

Additional anomalies

Additional anomalies are frequent but show no consistent features (trisomies and monosomies of various chromosomes, structural rearrangements including deletions and translocations).

Variants

t(9;12;14)(q34;p13;q22) (seen in conventional cytogenetics),
t(8;9;12)(p12;q34;p13) (seen in conventional cytogenetics),
ins(9;12)(q34;p13p13) (seen by molecular cytogenetics),
ins(12;9)(p13;q34q34) (seen by molecular cytogenetics).



Schematic diagram of the ETV6, ABL1 and ETV6-ABL1 proteins.

Genes involved and proteins

Note

As both genes have opposite orientation in relation to the centromeres, an in frame ETV6-ABL1 fusion gene requires at least three chromosomal breaks to be generated.

ETV6

Location

12p13

Note

The ETV6 gene encodes a transcription factor frequently rearranged in myeloid and lymphoid leukemias.

DNA/RNA

The ETV6 gene spans a region of less than 250 kb at band 12p13.1 and consists of 8 exons.

There are two start codons, one (exon 1a starting at codon 1) located at the beginning of the gene and another alternative (exon 1b starting at codon 43) upstream of exon 3.

Protein

The ETV6 protein (452 amino acids) contains two major domains, the HLH (helix-loop-helix) and ETS domains.

The HLH domain, also referred to as the pointed or sterile alpha motif domain, is encoded by exons 3 and 4 and functions as a homo-oligodimerization domain. The ETS domain, encoded by exons 6 through 8, is responsible for sequence specific DNA-binding and protein-protein interaction.

ABL1

Location

9q34

DNA/RNA

The ABL1 gene, spanning a 230-kb region at band 9q34, includes the 5' alternative first exons 1b and 1a and ten common exons numbered from 2 to 11. Alternative splicing using exons 1b and 1a gives rise to mRNA of 7 and 6 kb, respectively.

Protein

The ABL1 protein has three SRC homology (SH) domains called SH1, SH2 and SH3, of which SH1 that has a tyrosine kinase function.

The SH2 and SH3 domains are involved in protein-protein interactions, which regulate the tyrosine kinase activity; they are necessary for signal transduction function.

The ABL1 protein has also three nuclear localization signal domains and three DNA binding regions and an F-actin binding domain.

Result of the chromosomal anomaly

Hybrid gene

Transcript

Two ETV6-ABL1 transcripts were identified in most of the patients, one joining exon 5 of ETV6 to exon 2 of ABL1, the other, usually found at very low levels, joining ETV6 exon 4 to ABL1 exon 2.

Fusion protein

Description

The fusion protein retains all three SH domains, including the tyrosine kinase domain, of ABL1, which make these patients sensitive to tyrosine kinase inhibitors.

The retained N-terminal part of the ETV6 protein contains the helix-loop-helix domain necessary for oligomerization of the protein, which is required for tyrosine kinase activation, cytoskeletal localization and neoplastic transformation.

Oncogenesis

Constitutive tyrosine kinase activation of ABL1.

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