

Leukaemia Section

Short Communication

t(3;12)(q26;p13) ETV6/MECOM / t(3;12)(q26;p13) ETV6/EVI1

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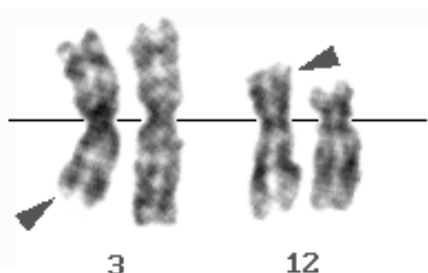
Abstract

Short communication on t(3;12)(q26;p13) ETV6/MECOM, with data on clinics, and the genes implicated.

Identity

Note

Only a few cases were shown to involve a ETV6/MECOM fusion by FISH or RT-PCR. In other cases, only MECOM or ETV6 was shown to be rearranged by FISH. Over-expression of MECOM/EVI1 was found in other cases. Finally, no cytogenetic or molecular analysis was performed in a few cases.



t(3;12)(q26;p13) G-banding - Courtesy Jean-Luc Lai and Alain Vanderhaegen. Clinics and pathology

Disease

Myeloid lineage: MDS in transformation, ANLL, BC-CML

Phenotype/cell stem origin

Multilineage involvement; MDS--> M0, M2, M4,

M7.

Epidemiology

46 cases described so far; sex ratio: 29M/16F (1 unknown); age: 2.5-87 yrs (med: 49 yrs), unknown age for 10 cases.

Cytology

Dysplasia of megakaryocytes, multilineage involvement.

Prognosis

See survival curve above.

Cytogenetics

Cytogenetics molecular

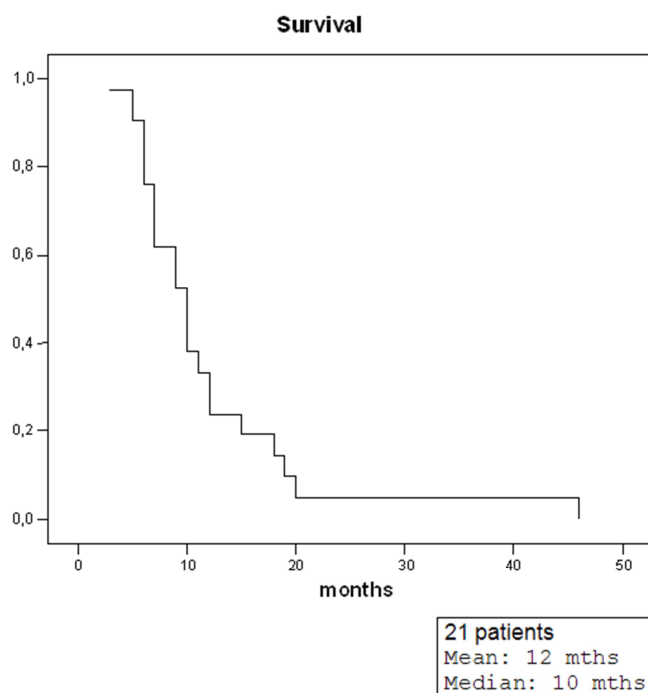
Heterogeneity of the EVI1 breakpoints, as evidenced by the Cytocell Aquarius EVI1 Breakapart probe.

The EVI1 Breakapart probe contains three probes: a probe labeled in Aqua of 562 kb in size centromeric to the EVI1 gene, a probe labeled in Spectrum Green of 181 kb covering EVI1 and its flanking regions and a probe labeled in Spectrum Orange of 124 kb telomeric of the EVI1 gene (telomeric of MYNN and covering LRRC34).

Additional anomalies

Sole anomaly in 22 cases.

Additional anomalies: t(9;22)(q34;q11) in 5 cases, -7/del(7q) in 11 cases, del(5q) in 2 cases, others in 6 cases.



Survival curve (21 patients, Mean: 12 mths, Median: 10 mths).

Genes involved and proteins

MECOM

Location

3q26

Note

Alias EVI1

DNA/RNA

MECOM is a "complex entity" made of two genes, EVI1 and MDS1.

EVI1 has 16 exons, of which 14 are coding, the start ATG codons being in exon 3.

MDS1 has 4 exons, exon 4 being located in the vicinity of exon 1 of EVI1.

Splicing of the second exon of MDS1 to the second exon of EVI1 leads to a MDS1-EVI1 mRNA.

Protein

EVI1 contains two domains of seven and three zinc finger motifs separated by a repression domain and an acidic domain at its C-terminus.

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 homooligodimerization domain. The ETS domain, encoded by exons 6 through 8, is responsible for sequence specific DNA-binding and protein-protein interaction.

Result of the chromosomal anomaly

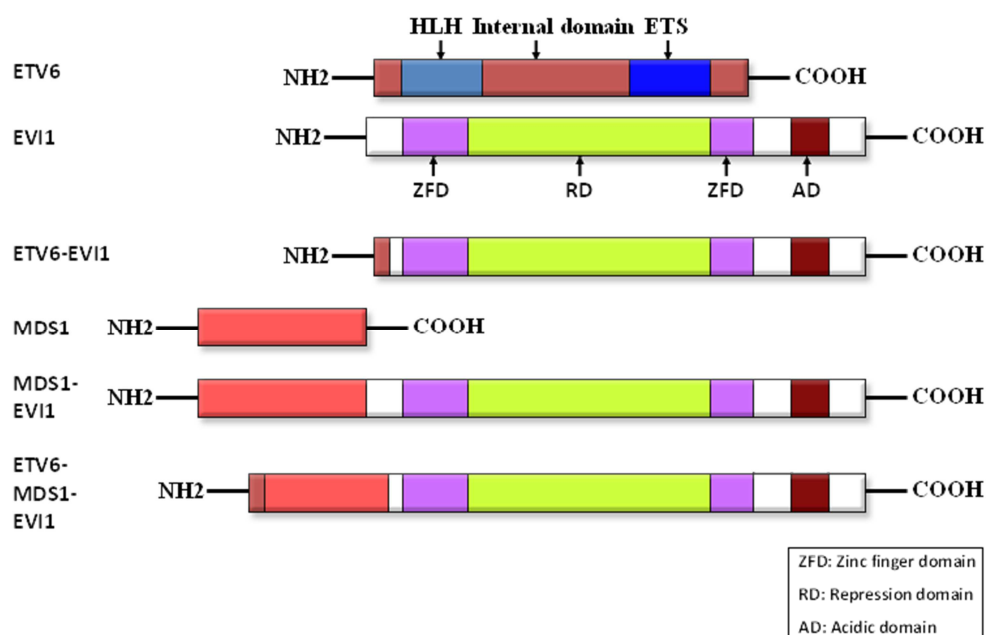
Hybrid gene

Description

Two mechanisms for generating the fusion gene, depending upon the involvement of the MDS1 gene.

Transcript

1) In-frame transcript consisting of the first two exons of ETV6 fused to MDS1 sequences, which in turn is fused to the second exon of the EVI1 gene.



Schematic diagram of the ETV6, EVI1, MDS1, MDS1-EVI1, ETV6-EVI1 and ETV6-MDS1-EVI1 proteins.

2) Out-of-frame fusion by direct fusion between exon 2 of ETV6 and exon 2 of EVI1, but keeping the open reading frame of EVI1 intact.

Fusion protein

Description

ETV6 contributes no known functional domain to the predicted chimeric protein but functional domains of EVI1 are retained.

Oncogenesis

The oncogenic potential of the translocation could be the result of the ETV6 promoter driving the transcription of EVI1. Because the ETV6 promoter is active in hematopoietic cells, this would result in inappropriate expression of the transcription factor EVI1.

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