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Leukaemia Section
Short Communication

inv(3)(q21q26)x2

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Identity

Other names
Double inversion of the long arm of chromosome 3

Note
Inv(3)(q21q26) is recognized as a distinctive entity of acute myeloid leukemia (AML) with recurrent genetic abnormalities of prognostic significance. The molecular consequence is the juxtaposition of the ribophorin I (RPN1) gene (located in band 3q21) with the ecotropic viral integration site 1 (EVI1) gene (located in band 3q26.2), resulting in over-expression of EVI1 (Bitter et al., 1985; Suzukawa et al., 1994).
Inv(3)(q21q26) in two copies is rare and was first described by Walter et al. in 1990.

Clinics and pathology

Disease

Myeloid malignancies

Note
This is a rare chromosomal rearrangement, described in only ten patients with myeloid diseases to date (Walter et al., 1990; Levy et al., 1994; Secker-Walker et al., 1995; Lee, 1999; Lahortiga et al., 2004; Toydemir et al., 2010; Lugthart et al., 2010; De Braekeleer et al., 2013).

Phenotype/cell stem origin

There were 2 cases of M1 acute myeloid leukemia (AML-M1), 2 cases of AML-M4, 3 cases of AML not otherwise specified, 2 cases of chronic myelogenous leukemia (CML) aberrant translocation, and 1 case of refractory anemia (RA).

Epidemiology

The sex ratio is balanced (5M/5F).
Median age, so far, is 62-65 years (range 36-83).

Evolution

Scarce data. One patient had a survival of 24 months (Lahortiga et al., 2004), a patient relapsed 6 months later and, eventually, died (survival: 9 months from diagnosis), and another one received standard induction chemotherapy without remission (survival: 4 months following diagnosis) (De Braekeleer et al., 2013).

Prognosis

Over-expression of EVI1 is a marker of poor prognosis in AML.

Cytogenetics

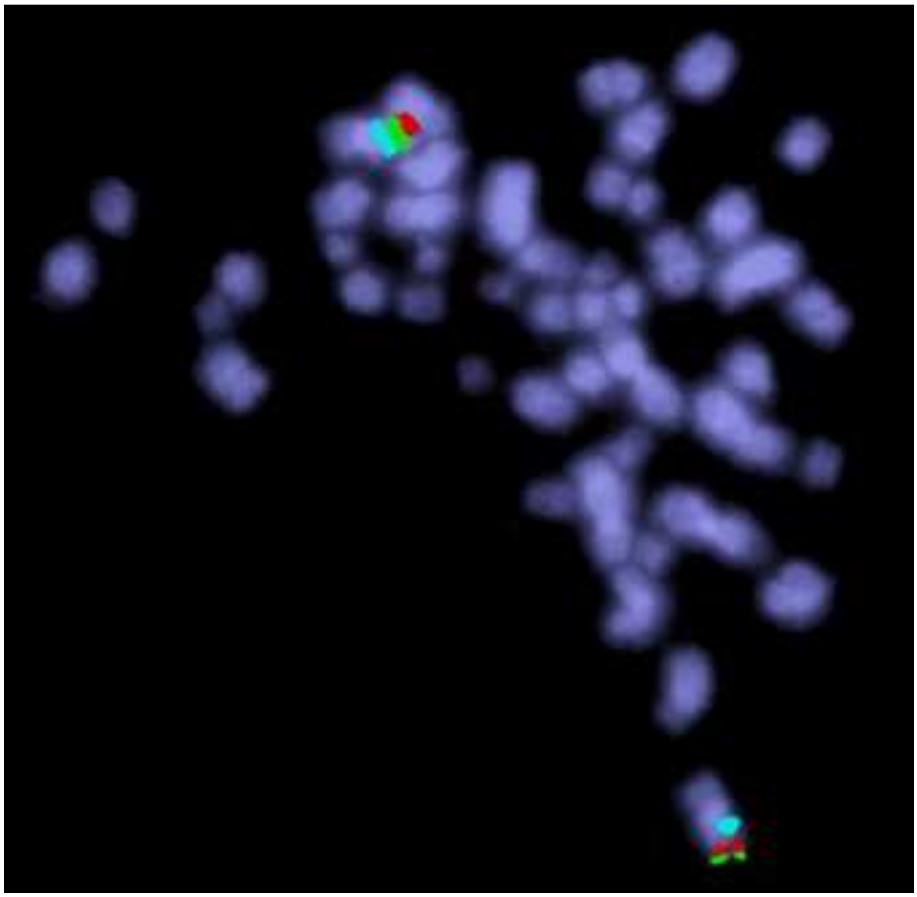
Partial karyotype showing the double inv(3)(q21q26) and monosomy 7.

Cytogenetics morphological

Double inv(3)(q21q26); additional anomalies including -7.

Cytogenetics molecular

Splitting of the probe and rearrangement of the three fluorochromes.



FISH with EVI1 Breakapart Cytocell Aquarius probe showing a normal chromosome 3 and an inverted chromosome 3.

Probes

The EVI1 Breakapart Cytocell Aquarius probe contains three probes: a probe (encompassing D3S3364/D3S1614) labeled in Aqua of 562 kb in size centromeric to the EVI1 gene, a probe (encompassing D3S1282) labeled in Spectrum Green of 181 kb covering EVI1 and its flanking regions and a probe (encompassing D3S3523) labeled in Spectrum Orange of 124 kb telomeric to the EVI1 gene (telomeric of MYNN and covering LRRC34).

Additional anomalies

-7/del(7q) was seen in 4 cases.

Genes involved and proteins

Note

The key event in the inv(3)(q21q26) is the overexpression of EVI1 (3q26).

EVI1

Location

3q26

Note

EVI1 is a nuclear transcription factor that plays an essential role in the proliferation and maintenance of hematopoietic stem cells and can inhibit myeloid differentiation.

Two alternative forms exists, one generated from EVI1, the other MECOM (MDS1 and EVI1 complex locus) through intergenic splicing with MDS1 (myelodysplasia syndrome 1), a gene located 140 kb upstream of EVI1.

DNA/RNA

EVI1 has 16 exons, of whose 14 are coding. Transcription can initiate from different alternative exons. Several splice variants of the EVI1 mRNA have been described.

Protein

The protein encoded by this gene is a transcriptional regulator involved in cell differentiation and proliferation, and apoptosis. The encoded protein can interact with transcriptional coactivators (P/CAF, CBP) and corepressors (CTBP1, HDAC) as well as other transcription factors (GATA1, Smad3).

RPN1 (ribophorin 1)

Location

3q21

DNA/RNA

RPN1 has 10 exons. Transcription leads to 8 alternative transcripts, of whose 2 are protein coding.

Protein

This protein, which is a type I integral membrane protein found only in the rough endoplasmic reticulum, constitutes part of the regulatory subunit of the 26S proteasome. It may mediate binding of ubiquitin-like domains to this proteasome.

Result of the chromosomal anomaly

Hybrid gene

Description

RPN1 enhancer juxtaposed to EVI1.

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