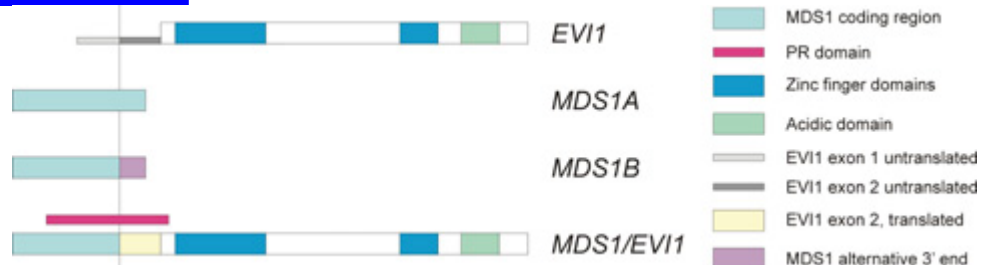


3q rearrangements in myeloid malignancies

Identity



Clinics and Pathology

Disease	In myeloid malignancies (acute myeloid leukemia (AML), myelodysplastic syndromes (MDS), chronic myelogenous leukemia (CML) as well as other myeloproliferative disorders), involvement of 3q26 in balanced rearrangements is highly suggestive of EVI1 and/or MDS1/EVI1 rearrangement. As a consequence, balanced aberrations involving 3q26 are mainly detected in myeloid malignancies.
Epidemiology	3q26 rearrangements have been described in up to 5% of unselected patients with myeloid malignancies.
Clinics	Often associated with young age at diagnosis, trilineage dysplasia, dysmegakaryopoiesis and prior treatment with alkylating agents.
Evolution	In CML, emergence of an additional Ph+ clone with a 3q26 rearrangement can be indicative of a pending disease transformation.
Prognosis	Generally 3q26 rearrangements are associated with adverse prognosis. This adverse prognosis probably correlates to the highly increased EVI1 expression, detectable in the vast majority of these patients. Whether 3q26 rearrangements, which are not associated with ectopic EVI1 expression share the same prognostic features, however, has not been addressed.

Cytogenetics

Cytogenetics Although the frequently occurring balanced 3q26 rearrangements can be readily identified by G-, Q-, or R-banding, the distal localisation makes it a good candidate for involvement in cryptic aberrations. Rearrangements in which EVI1 and or MDS1/EVI1 involvement have been well established include: CYTOGENETICS_MORPHOL

[t\(3;3\)\(q21;q26\)](#)
[inv\(3\)\(q21q26\)](#)
[ins\(3\)\(q26;q21q26\)](#)
[t\(3;12\)\(q26;p13\)](#)
[t\(3;21\)\(q26;q22\)](#)

Recently we demonstrated EVI1 involvement in other recurrent rearrangements such as :

[t\(2;3\)\(p13-p23;q26\)](#)

t(3;6)(q26;q25).
t(3;13)(q26;q14)
t(3;17)(q26;q22)

In addition, EVI1 is involved in more rare rearrangements such as

inv(3)(p12q26)
inv(3)(q23q26)
t(3;3)(p24;q26)
t(3;5)(q26;q34)
t(3;9)(q26;p23)
t(3;12)(q26;q21)
t(3;18)(q26;q11).

One should be aware of the fact, however, that in the majority of patients demonstrating ectopic EVI1 expression, 3q26 rearrangements are generally not detectable cytogenetically. Whether in these patients cryptic aberrations cause EVI1 deregulation is currently under investigation.

Cytogenetics Molecular	Breakpoint heterogeneity, with breakpoints mapping 3 \bar{O} as well as 5 \bar{O} , of EVI1 impeded a sensitive detection of EVI1 rearrangement using molecular cytogenetic techniques. Recently, however, we studied numerous 3q26 rearrangements using a 1.3Mb contig covering the EVI1 locus. We demonstrated sensitive and specific detection of EVI1 rearrangements using dual colour FISH using the following probe combinations: RP11-82C9 and RP11-694D5 for 5 \bar{O} rearrangements and RP11-82C9 and RP11-362K14 for 3 \bar{O} rearrangements.
Additional anomalies	3q26 rearrangements are frequently associated with monosomy 7 and complex chromosomal aberrations.

Genes involved and Proteins

Gene Name [EVI1](#), MDS1/EVI1 and MDS1

Location 3q26.2

Note EVI1 and MDS1 display intergenic splicing, creating a PR domain member, MDS1/EVI1. Analogously to other PR domain genes, such as RIZ, MDS1/EVI1 and EVI1 are hypothesised to display antagonistic properties. Currently, experimental data are limited and conflicting indicating that further experiments are needed to clarify the exact role of both evolutionary conserved transcripts.
The different transcripts encoded by the EVI1 locus.

Dna / Rna	EVI1 spans approximately 50 kb and contains 12 exons, 10 of which are coding. Translation starts in exon 3. MDS1/EVI1 results from intergenic splicing from MDS1 and EVI1, the resulting transcript MDS1/EVI1, contains the 2 first MDS1 exons spliced in frame to EVI1 exon 2.
Protein	The MDS1 gene spans approximately 230kb. The EVI1 gene encodes a sequence specific Cys2/Hys2 type 145kDa zinc finger protein, containing two sets of seven and three zing fingers, respectively. Alternative splicing creates a 88 kDa isoform that lacks the nuclear localisation signal and two zinc fingers. MDS1/EVI1 encodes a PR domain family member. The PR domain is suggested to play an

inhibiting role in tumorigenesis.

Result of the chromosomal anomaly

Hybrid gene Note Ectopic expression of an intact or truncated EVI1 transcript has been reported as a result of 3q26 rearrangements. Generally, 3q26 breakpoints map 3' to EVI1 in the inv(3) while the t(3;3) breakpoints more frequently reside 5' to EVI1. In addition expression of GR6/EVI1 and RPN1/EVI1 chimeras have been described in the t(3;3). Alternatively, [AML1](#)/MDS1, AML1/MDS1/EVI1 and AML1/EVI1 fusion transcripts are produced by the t(3;21)(q26;q22), while [ETV6](#)/MDS1/EVI1 and ETV6/EVI1 fusions are related to the t(3;12)(q26;p13). The net effect of these rearrangements comprises an EVI1 gain of function: as a result of EVI1 ectopic expression or resulting from MDS1/EVI1 inactivation by disruption of its PR domain.

Several hybrid genes resulting from 3q26 rearrangements have been characterised and cloned, including the AML1/MDS1/EVI1 from the t(3;21)(q26;q22) and the ETV6/MDS1/EVI1 in the t(3;12)(q26;p13) these rearrangements are discussed elsewhere in the Atlas.

External links

[Probe](#) ([AC078985](#))

[Probe](#) ([AC112911](#))

[Probe](#) ([AC078795](#))

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