**Atlas of Genetics and Cytogenetics in Oncology and Haematology**

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# Gene Section
**Review**

# EVI1 (ecotropic viral integration site 1 (EVI1) and myelodysplastic syndrome 1 (MDS1)-EVI1)

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## Identity

**Hugo:** EVI1
**Other names:** PRDM3
**Location:** 3q26.2

## DNA/RNA

### *Description*

The human EVI1 gene spans approximately 65 kb of genomic DNA. 14 of its 16 exons are coding (Fig. 1A). Transcription can initiate from alternative exons 1a, 1b, 1c, 1d, or 3L (Fig. 1B), and several alternative splice variants of the EVI1 mRNA have been described (Delta324, -Rp9, Delta105; Fig. 1A).
The human MDS1 gene consists of 4 exons spread over a genomic region of more than 500 kb. MDS1 exon 4 is located less than 2 kb upstream of EVI1 exon1a. The MDS1-EVI1 mRNA presumably results from splicing of the second exon of MDS1 to the second exon of EVI1 (Fig. 1B).

### *Transcription*

Telomere to centromere.

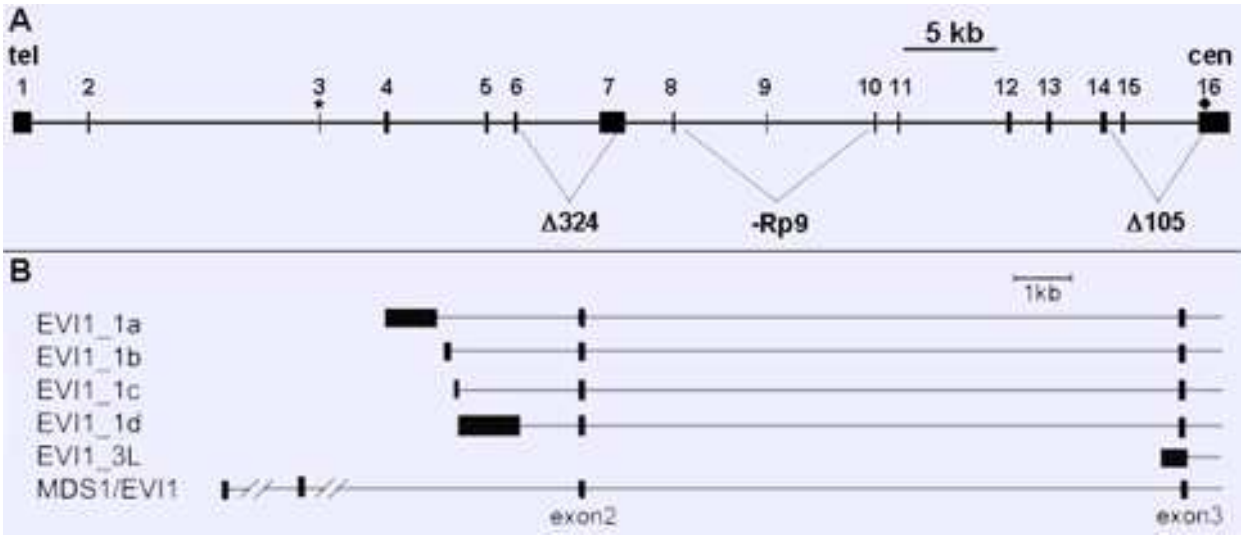



Figure 1. Genomic locus of the human EVI1 gene and EVI1 mRNA variants. Asterisk, translation initiation codon; diamond, translation stop codon. (This figure was reprinted from Gene 396, R. Wieser, 'The oncogene and developmental regulator EVI1: Expression, biochemical properties, and biological functions', pages 346-357, Copyright Elsevier (2007), with permission from Elsevier. Gene homepage: http://www.sciencedirect.com/science/journal/03781119).

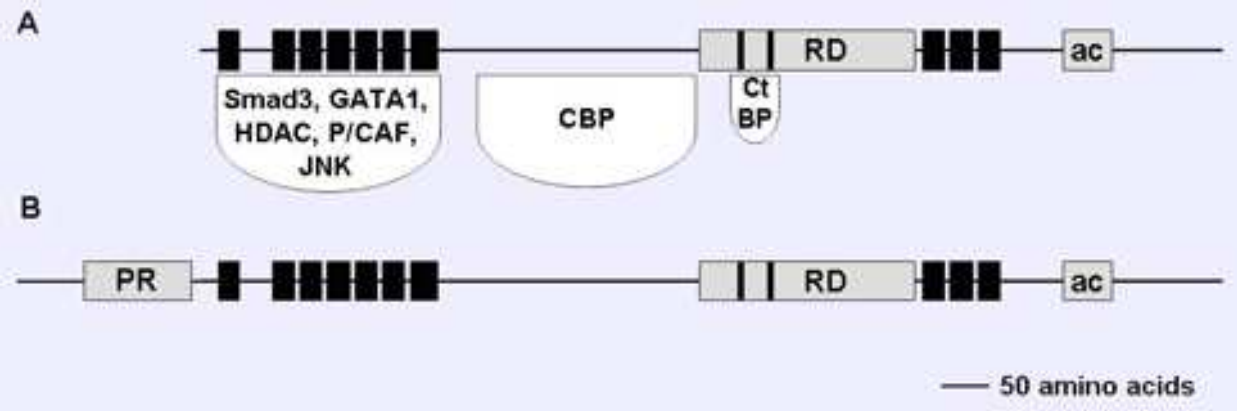



Figure 2. A) EVI1 and B) MDS1/EVI1 protein domains and EVI1 interacting proteins. Black boxes, zinc finger motifs; RD, repression domain, with binding motifs for the transcriptional corepressor CtBP depicted as black bars; ac, acidic region; PR, PR domain. This figure was reprinted from Gene 396, R. Wieser, 'The oncogene and developmental regulator EVI1: Expression, biochemical properties, and biological functions', pages 346-357, Copyright Elsevier (2007), with permission from Elsevier. Gene homepage: http://www.sciencedirect.com/science/journal/03781119.

# Protein

## Description

Exon 3 of the human EVI1 gene contains two closely spaced ATG codons, either of which may serve as the translation initiation site. Depending on which ATG is used, proteins of 1051 or 1041 amino acids will be formed. EVI1 contains two domains of seven and three zinc finger motifs, respectively, a repression domain between the two sets of zinc fingers, and an acidic domain of unknown function at its C-terminus. It is a 145 kDa protein that is capable of binding to DNA in a sequence specific manner, and that interacts with transcriptional coactivators (P/CAF, CBP) and corepressors (CtBP, HDAC) as well as other sequence specific transcription factors (GATA1, Smad3).

Predicted translation of MDS1-EVI1 adds 188 amino acids to the N-terminus of EVI1. 63 of these additional amino acids are derived from the untranslated second exon and the untranslated part of the third exon of EVI1, and the remaining 125 from the MDS1 gene. MDS1-EVI1 contains a PR domain, which is about 40% homologous to the N-terminus of the retinoblastoma-binding protein, RIZ, and the PRDI-BF1 transcription factor. Some biological functions of MDS1/EVI1 are different from, or even antagonistic to, those of EVI1.

## Expression

In human tissues/organs, the EVI1 mRNA is expressed abundantly in kidney, lung, pancreas, stomach, ovaries, uterus, and prostate, to a lesser extent in the small intestine, colon, thymus, spleen, heart, brain, testis, and placenta, and at very low levels in skeletal muscle and bone marrow. The pattern of expression of MDS1-EVI1 is very similar to that of EVI1.

In the adult mouse, the Evi1 mRNA is expressed, at varying levels, in the kidney, lung, stomach, ovary, uterus, intestine, thymus, spleen, heart, brain, and liver. In the mouse embryo, Evi1 mRNA levels are high in the urinary system and Mullerian ducts, the lung, the heart, and the emerging limb buds.

Similar Evi1 expression patterns were also observed in Xenopus, chicken, and zebrafish.

## Localisation

Nuclear; in part in speckles.

## Function

Because of the spatially and temporally restricted expression of EVI1, it has been suggested that this gene plays an important role in development and could be involved in organogenesis, cell migration, cell growth, and differentiation.

In the mouse, homozygous disruption of the 6th exon of the Evi1 gene lead to embryonic lethality, with widespread hypocellularity, reduced body size, small or absent limb buds, a pale yolk sac and placenta, abnormal development of the nervous system and the heart, and massive haemorrhaging.

EVI1 is thought to exert its biological functions mainly by acting as a transcription factor. In addition, however, EVI1 has been reported to inhibit c-jun N-terminal kinase, and to stimulate PI3K/AKT signalling.

## Homology

EVI1 orthologs are present in many species. Evi1 proteins from other mammals share more than 90% amino acid sequence identity with the human protein, and Xenopus Evi1 is 77% identical to its human counterpart. MDS1-EVI1 shares an overall homology with the C. elegans Egl 43 protein that includes the PR domain at the N-terminus and the two zinc-finger domains. An MDS1/EVI1 ortholog, hamlet, is also present in Drosophila.

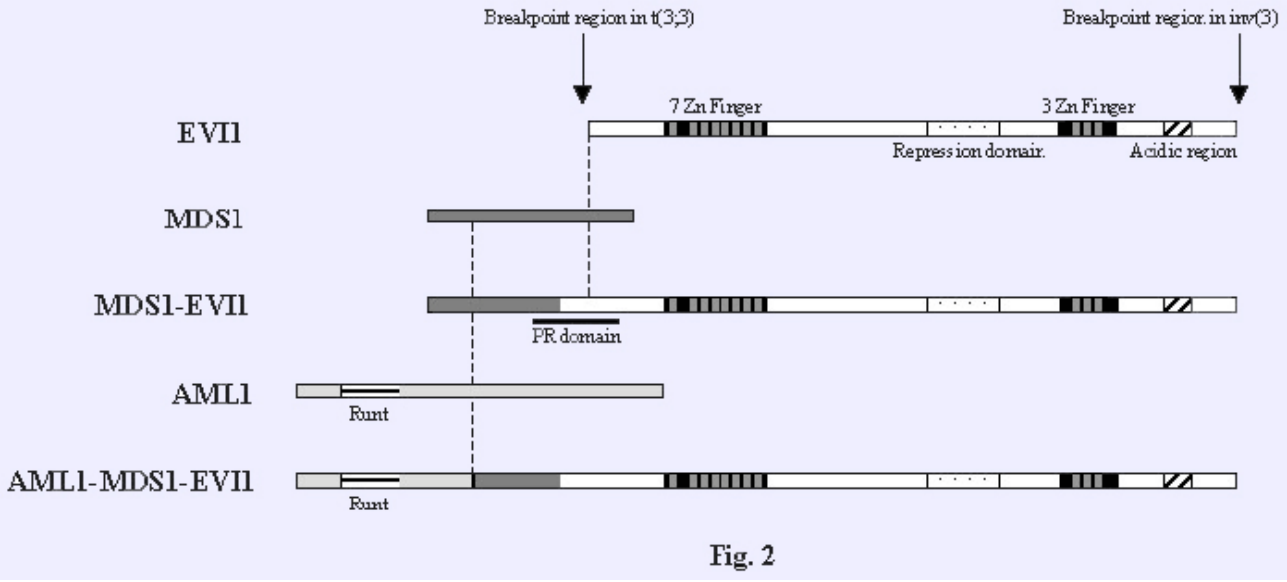



Figure3. Normal and leukemia-associated EVI1 protein variants.

# Implicated in

## *t(3;3)(q21;q26) or inv(3)(q21q26)*

**Note:** 3q21q26 syndrome. Chromosomal rearrangements located either 5' or 3' of the EVI1 gene can activate its transcription in haematopoietic cells. Usually, t(3;3)(q21;q26) breakpoints are located 5' of EVI1, and inv(3)(q21q26) breakpoints 3' of it. Nevertheless, in both cases aberrant expression of the EVI1 gene may be due to its juxtaposition to the enhancer of the constitutively expressed housekeeping gene ribophorin 1 at 3q21.

**Disease**

Acute Myelogenous Leukemia (AML), Myelodysplastic Syndrome (MDS), and Chronic Myelogenous Leukemia (CML).

**Prognosis**

Patients with EVI1 rearrangements have elevated platelet counts, marked hyperplasia with dysplasia of megakaryocytes, and a poor prognosis.

**Cytogenetics**

Rearrangements at 3q26 may occur as a sole anomaly, but are often associated with monosomy 7 or deletion of the long arm of chromosome 7, and, less frequently, deletion in chromosome 5.

**Oncogenesis**

Inappropriate expression of EVI1 in haematopoietic cells alters differentiation into granulocytes, erythrocytes and megakaryocytes. EVI1 promotes the proliferation of certain cell types, but inhibits the growth of others. It interferes with growth inhibition by TGF-b and with apoptosis elicited by a variety of stimuli. In a murine bone marrow transduction/transplantation model, EVI1 caused a disease resembling human myelodysplastic syndrome. Additional coexpression of Hoxa9 and Meis 1 lead to overt leukemia.

## *t(3;21)(q26;q22)*

**Disease**

Therapy-related MDS/AML and CML during the blast crisis.

**Prognosis**

Poor.

**Cytogenetics**

Complex.

**Abnormal Protein**

AML1 -MDS1-EVI1.

**Oncogenesis**

AML1-MDS1-EVI1 is a chimeric transcription factor that interferes with AML1 functions in a dominant negative manner, but shares some biological effects with EVI1.

## *t(3;12)(q26;p13)*

**Disease**

CML during the blast crisis and MDS in transformation.

**Prognosis**

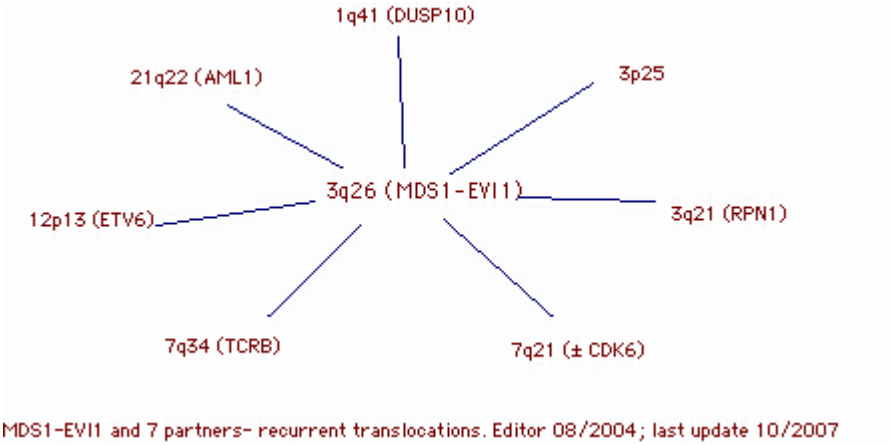
Poor.

**Cytogenetics**

Complex.

**Abnormal Protein**

Overexpression of a fusion protein between the amino terminus of TEL, which does not contain any functional domains, and the entire MDS1/EVI1 protein is driven by the TEL promoter.




MDS1-EVI1 and 7 partners- recurrent translocations. Editor 08/2004; last update 10/2007

### *AML without 3q26 rearrangements.*

**Note:** EVI1 may also be overexpressed in AML, MDS, or CML in blast crisis in the absence of any cytogenetically detectable 3q26 rearrangements.

**Disease**

AML, MDS, CML.

**Prognosis**

Poor (AML).

**Oncogenesis**

As above.

## Breakpoints

**Note:** Other chromosomal rearrangements that results in the inappropriate expression of EVI1 include t(2;3)(p13;q26), t(2;3)(q23;q26), t(3;7)(q27;q22), t(3;8)(q26;q24), t(3;13)(q26;q13-14), and t(3;17)(q26;q22).

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