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Leukaemia Section
Short Communication

inv(12)(p13q15) ETV6/PTPRR

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Clinics and pathology

Disease

Myelodysplastic syndrome (MDS), and acute myeloid leukemias (AML)

Clinics

A 75-year-old female patient presented with refractory anemia (RA) (Welborn et al., 2004). A 24-year-old female patient presneted with acute myelogenous leukemia (M2-AML) (Nakamura et al., 2005).

Prognosis

The patient with RA was alive 14 months after diagnosis without treatment. The patient with M2-AML underwent bone marrow transplantation and remained in remission 44 months after diagnosis.

Genetics

Note

Another case of inv(12)(p13q15) was that of a 59 - year-old female patient with AML M2. However, the 5' part of ETV6 was translocated to chromosome15 and the 3' part of ETV6 to 12q15 (Setoyama et al., 1998). Therefore the genetic rearrangement is different.
Only the case studied by Nakamura et al., 2005 ascertained the breakpoints within ETV6 and PTPRR.

Cytogenetics

Additional anomalies

+8 and additional abnormalities were present in the RA case; the inv(12) was the sole anomaly in the M2-AML case.

Genes involved and proteins

ETV6

Location

12p13

Protein

452 amino acids. ETV6 is composed of a HLH domain responsible for hetero- and homodimerization in N-term, and an ETS domain responsible for sequence specific DNA-binding in C-term (binds to the DNA sequence 5'-CCGGAAGT-3'). Transcriptional regulator; tumor suppressor. Involved in bone marrow hematopoiesis.

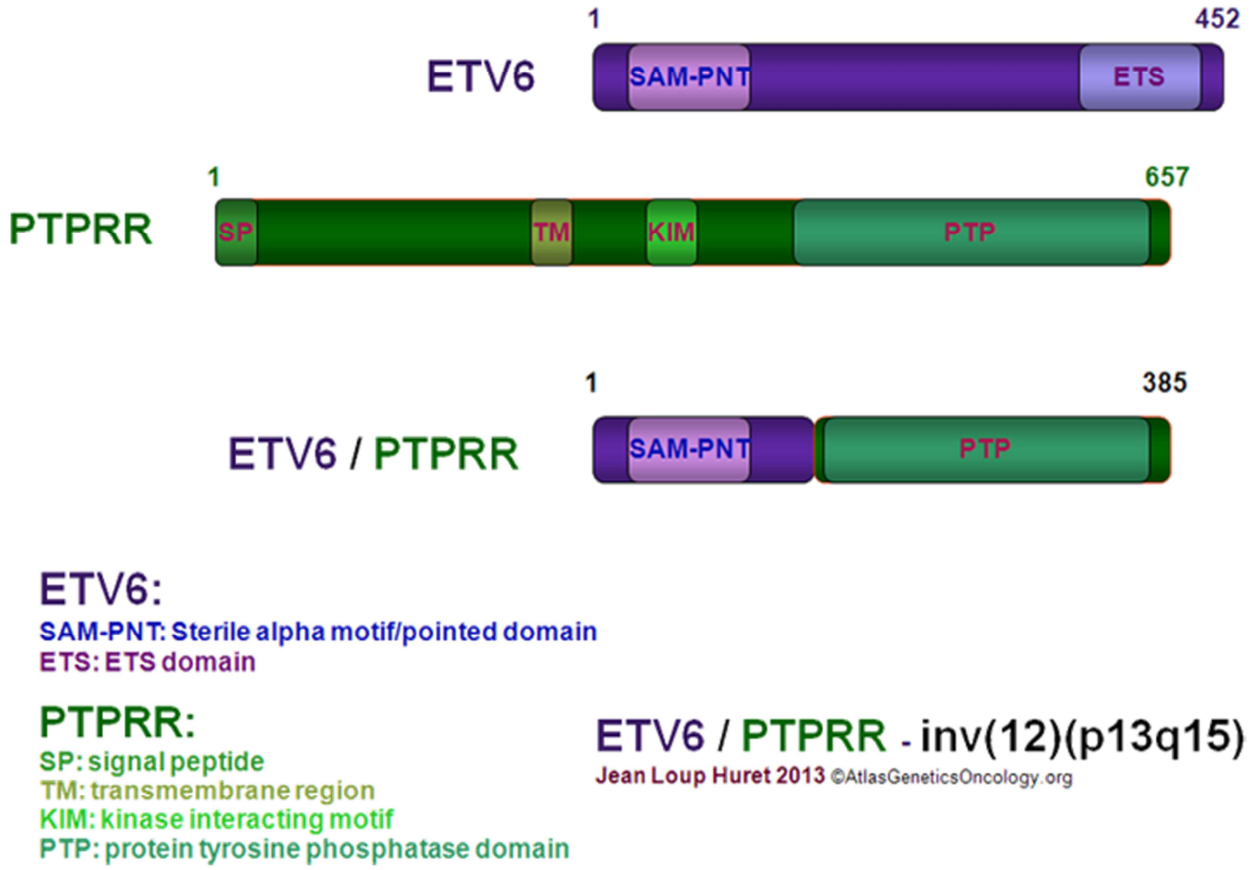
PTPRR

Location

12q15

Protein

657 amino acids. PTPRR belong to the protein tyrosine phosphatase (PTP) family. PTPRR is composed of a signal peptide, a hydrophobic region, a transmembrane region, a kinase interacting motif, and a protein tyrosine phosphatase domain. PTPRR isoforms are regulators of MAPK phosphorylation levels. Activated PKA prevents the PTPRR-MAPK binding and MAPK inhibition by phosphorylation of the KIM domain of PTPRR. PTPRR-deficient mice exhibit ataxic symptoms (Hendriks et al., 2009). PTPRR is down regulated in colorectal cancer (Menigatti et al., 2009).



Result of the chromosomal anomaly

Hybrid gene

Description

The chimeric DNA joined ETV6 exons 1 to 4 and PTPRR exons 7 to 14.

Alternative splicing leads to generation of 10 ETV6/PTPRR chimeric cDNAs, of which a truncated ETV6, due to frameshift, and an ETV6/PTPRR in-frame isoform with an open reading frame of 1158 nucleotides coding for 385 amino acids, including the helix-loop-helix domain of ETV6 and most of the protein tyrosine phosphatase domain of PTPRR.

Fusion protein

Description

The ETV6/PTPRR fusion protein is made of 385 amino acids (aa), including the helix-loop-helix domain of ETV6 and most of the protein tyrosine phosphatase domain of PTPRR. 154 aa come from ETV6 and 231 from PTPRR.

Oncogenesis

Both truncated ETV6 and ETV6/PTPRR were shown to affect nuclear localization of wild-type ETV6. Both can heterodimerize with wild-type ETV6. ETV6/PTPRR lacks protein tyrosine phosphatase activity. Both truncated ETV6 and ETV6/PTRPP could be important in leukemogenesis.

References

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