

Leukaemia Section

Short Communication

t(5;9)(q32;p24) KANK1/PDGFRB

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Published in Atlas Database: October 2012

Online updated version: <http://AtlasGeneticsOncology.org/Anomalies/t0509q32p24ID1612.html>
DOI: 10.4267/2042/48497

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Clinics and pathology

Disease

Myeloproliferative neoplasm with essential thrombocythemia

Note

No detectable BCR-ABL transcript or JAK2 V617F mutation.

Epidemiology

Found in one case of myeloproliferative neoplasm with severe thrombocythemia, in a 67-year-old male.

Clinics

Thrombocythemia (platelets, $904 \times 10^9/l$) without prominent eosinophilia or neutrophilia.

Cytology

Increased number of polymorphic megakaryocytes without any blast cells or dysplastic features; suggestive of myeloproliferative neoplasm, most likely essential thrombocythemia.

Treatment

No response to hydroxyurea, complete remission with imatinib at the dose of 100 mg/day.

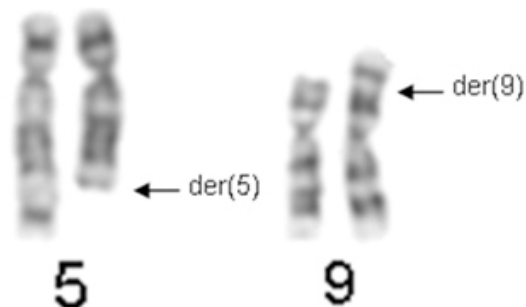
Evolution

Complete remission (FU: 3 years).

Prognosis

Unknown.

Cytogenetics

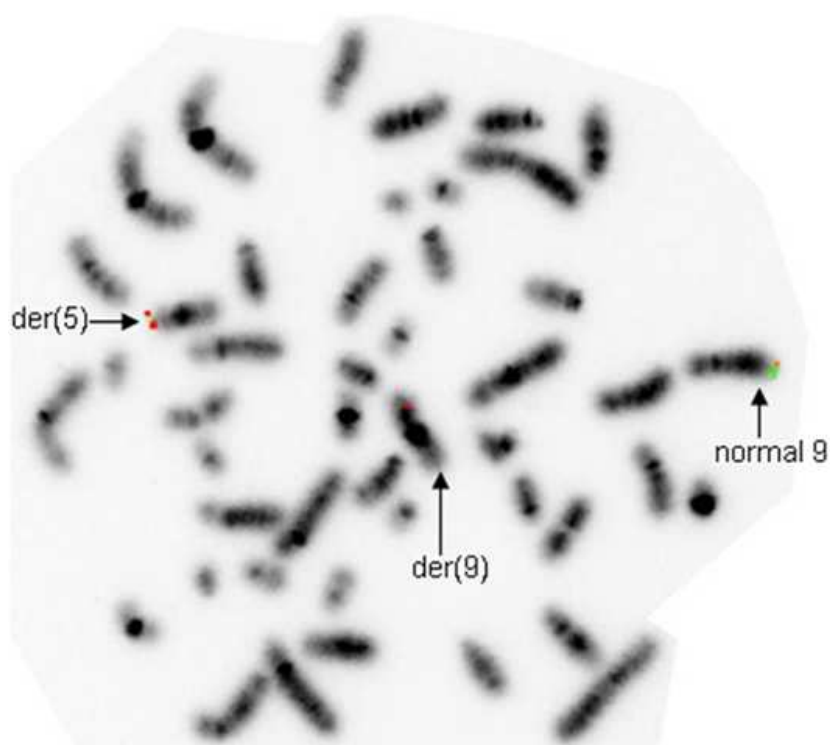


Cytogenetics morphological

46,XY,t(5;9)(q31~32;p22~?24.3)[16]/46,XY[2].

Cytogenetics molecular

Disruption of PDGFR β (5q31~32) and KANK1 (9p24.3) loci.



FISH analysis using the RP11-130C19 and RP11-31F19 probes. RP11-130C19 is split between the der(5) and the der(9), while RP11-31F19 is translocated to the der(5).

Probes

RP11-130C19 and RP11-31F19.

Additional anomalies

No.

Genes involved and proteins

KANK1 (KN motif and ankyrin repeat domains 1)

Location

9p24.3

Note

Formerly: KANK, ANKRD15, KIAA0172.

Protein

Two KANK1 protein isoforms are encoded by different transcripts of the same gene: a long isoform of 1352 amino-acids and a short one 1194 aa, which is predominant in hematopoietic cells (Medves et al., 2010).

Both isoforms have multiple N-terminal coiled-coil domains, which are included in the fusion with PDGFRB, and C-terminal ankyrin repeat domains (Kakinuma et al., 2009).

PDGFRB (platelet-derived growth factor receptor, beta polypeptide)

Location

5q31-33

Protein

Platelet-derived growth factors (PDGF) receptor, beta isoform. This receptor belongs to the receptor tyrosine kinase family (type III).

Result of the chromosomal anomaly

Hybrid gene

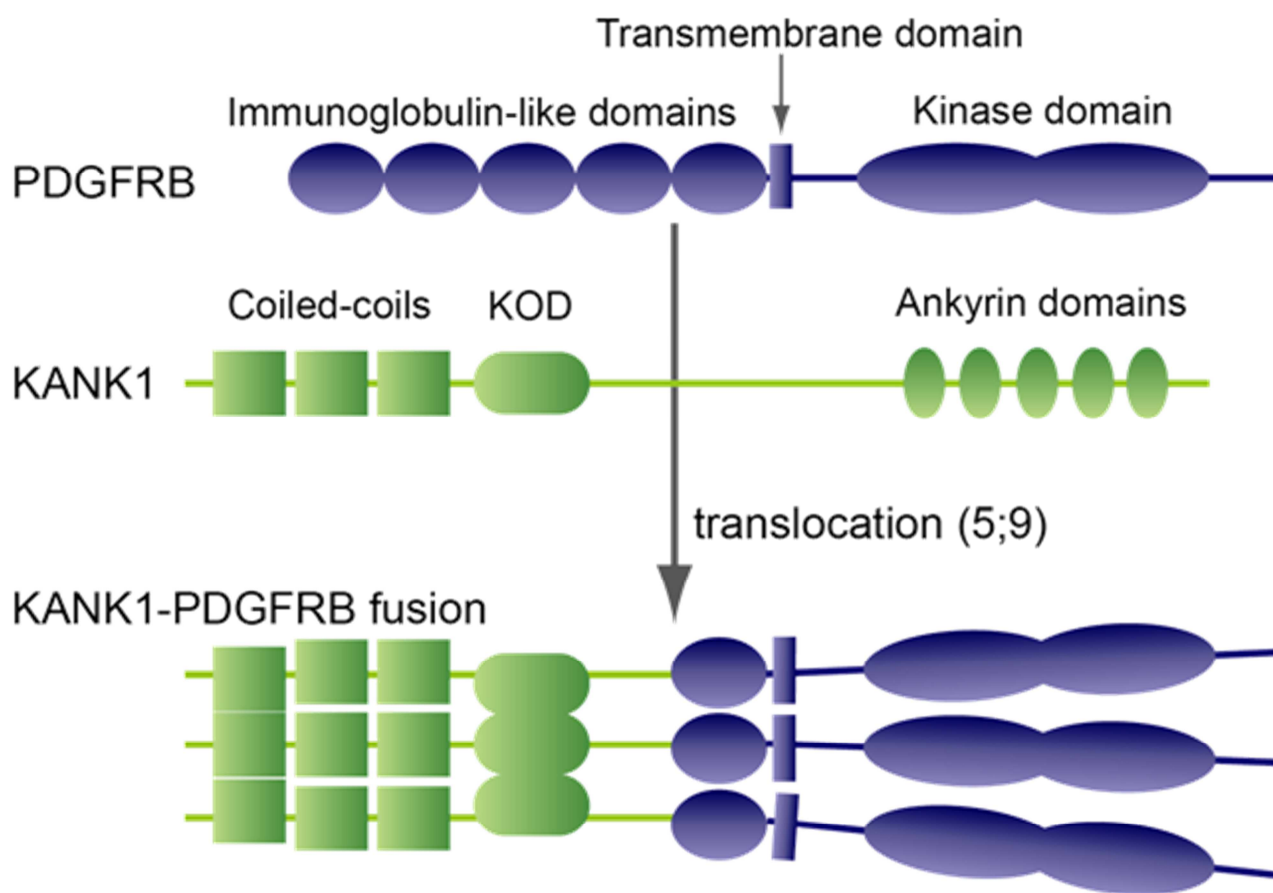
Description

Exon 2 of KANK1 (ENST00000382293, Ensembl database, up to nucleotide 3020) is fused to exon 9 of PDGFRB (ENST00000261799, from nucleotide 1714).

Fusion protein

Description

The fusion protein contains the first 741 residues of KANK1 fused to the last 692 residues of PDGFRB (Medves et al., 2010). This includes several coiled-coil domains of KANK1 and the fifth immunoglobulin-like domain, the transmembrane domain and the kinase domain of PDGFRB. The deletion of the immunoglobulin-like domain does not affect the oncogenic activity of the fusion (Medves et al., 2010). By contrast, deletion of the coiled-coil domains prevents cell transformation and signaling via STAT5 and MAP kinases (Medves et al., 2011). Our data suggest that KANK1-PDGFRB adopts a trimeric and multimeric conformation (Medves et al., 2011).



Structure of PDGFRB, KANK1 and the KANK1-PDGFRB fusion. See text for details. KOD, KANK1 oligomerization domain. Adapted from Demoulin et al., 2012 and Medves et al., 2012.

Oncogenesis

This fusion protein induces the proliferation of Ba/F3 cells (Medves et al., 2010) and CD34⁺ human progenitors (Medves et al., 2011).

The fusion was identified in thrombocythemia, which is associated with JAK2 mutations or indirect activation of JAK2 by mutated thrombopoietin receptors (c-MPL).

In the present case, no JAK2 activation was detected in cells expressing KANK1-PDGFRB and these cells are not sensitive to JAK inhibitors (Medves et al., 2011).

Instead, they are highly sensitive to imatinib.

References

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This article should be referenced as such:

Duhoux FP, Medves S, Noël L, Ferrant A, Poirel HA, Demoulin JB. t(5;9)(q32;p24) KANK1/PDGFRB. *Atlas Genet Cytogenet Oncol Haematol*. 2013; 17(2):129-131.