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Leukaemia Section
Mini Review

t(5;14)(q33;q24)

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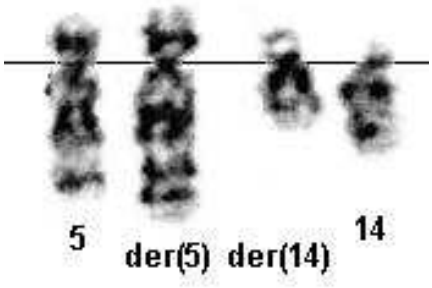
Identity



G-band analysis. Partial karyotype showing the t(5;14)(q33;q24).

Clinics and pathology

Disease

CML-like myeloproliferative disorder.

Note

L Atypical CML.

Epidemiology

Very rare, only one case described.

Clinics

Eosinophilia, basophilia, psoriasic skin lesions, splenomegaly.

Treatment

Imatinib mesylate after 14 years from diagnosis.

Evolution

Molecular remission after one year of treatment.

Prognosis

Good.

Cytogenetics

Additional anomalies

Sole anomaly.

Variants

No variants described.

Genes involved and proteins

NIN

Location

14q22.1

Note

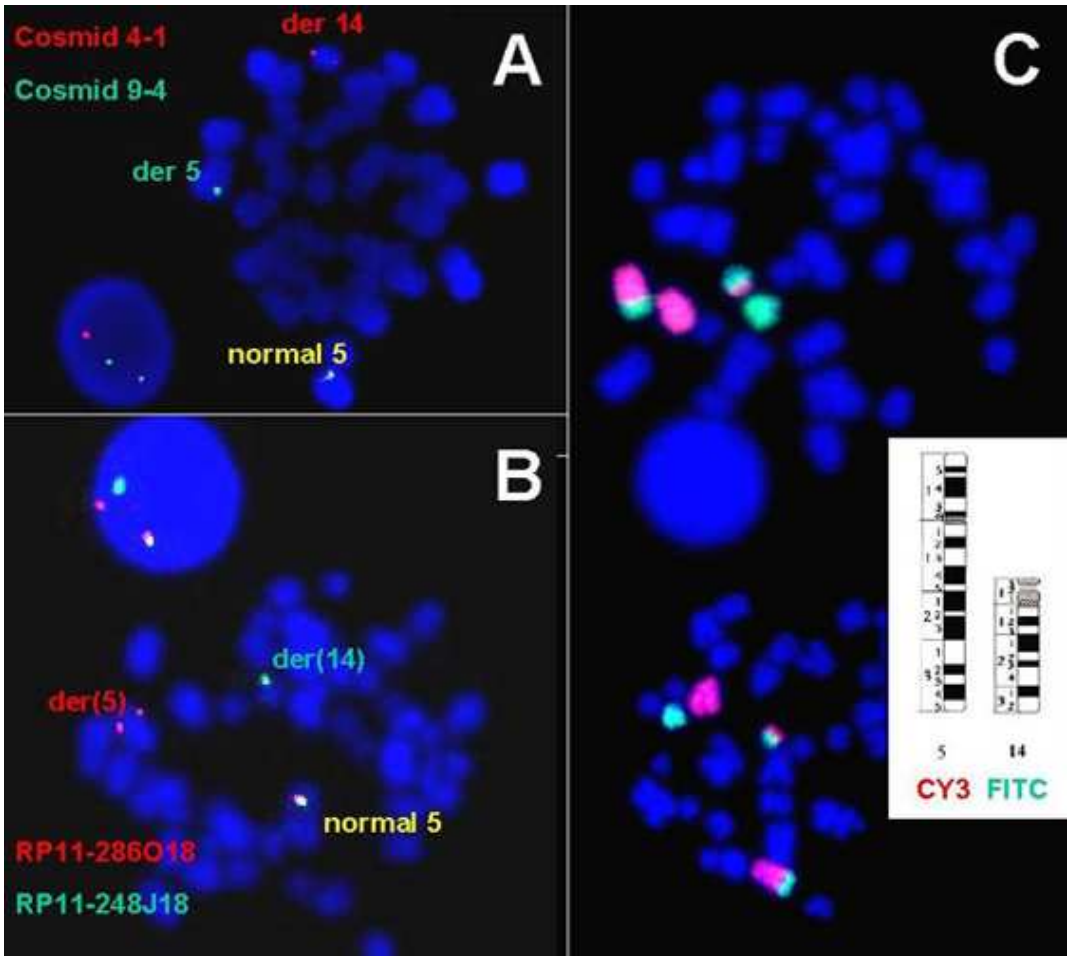
This gene is involved only in this translocation.

DNA/RNA

31 exons spanning 111.3 Kb on 14q22.1. Transcription is from telomere to centromere. 4-5 alternative transcripts.

Protein

Homooligomer. Interacts with GSK3B (GSK3-beta) via its C-terminus domain, it also interacts with C14ORF166 preventing its phosphorylation by GSK3-beta. NIN is a component of the core centrosome. Arranged in a tubular conformation with an open and a closed end within the centrosome. In the mother centrosome, it localizes at both ends of the centrosome tube, including the site of centrosome duplication, while in the daughter centrosome it is present only at the closed end. Requires PCM1 for centrosome localization. In interphase cells, it is localized in the centrosome. Decreases in metaphase and anaphase and reappears in telophase. Its expression is ubiquitous and is high in heart and skeletal muscle.



FISH analyses:
(A) FISH using cosmids 9-4 (green) and 4-1 (red) showing the putative involvement of PDGFRB in the translocation.
(B) FISH using BACs RPCI-11 286O18 (red, centromeric to NIN) and RPCI-11 248J18 (covering almost all NIN) showing a split between them compatible with the molecular breakpoint found.
(C) FISH painting using STAR*FISH human whole chromosome specific probes for chromosomes 5 (Cy3, red) and 14 (FITC, green) which confirms the translocation between them.

PDGFRB

DNA/RNA

23 exons spanning 42 Kb on 5q32. Transcription is from telomere to centromere. 1 transcript with 5.6 Kb.

Protein

This gene encodes a cell surface tyrosine kinase receptor for members of the platelet-derived growth factor family. These growth factors are mitogens for cells of mesenchymal origin. The identity of the growth factor bound to a receptor monomer determines whether the functional receptor is a homodimer or a heterodimer, composed of both platelet-derived growth factor receptor alpha and beta polypeptides. This gene is flanked on chromosome 5 by the genes for granulocyte-macrophage colony-stimulating factor (GM-CSF) and macrophage-colony stimulating factor receptor; all three genes may be implicated in the 5q-syndrome. Several rare translocations between this gene and other partners result in chronic eosinophilic leukemia, atypical CML or chronic myelomonocitic leukemia with eosinophilia. Only one case with a t(5;14)(q31;p12) and CEV14-PDGFRB fusion has been found as a secondary event in a patient with relapsed acute myeloid leukemia.

Result of the chromosomal anomaly

Hybrid gene

Description

Fusion in-frame between NIN exon 28 and PDGFRB exon 12.

Transcript

5' NIN-PDGFRB 3'.

Detection

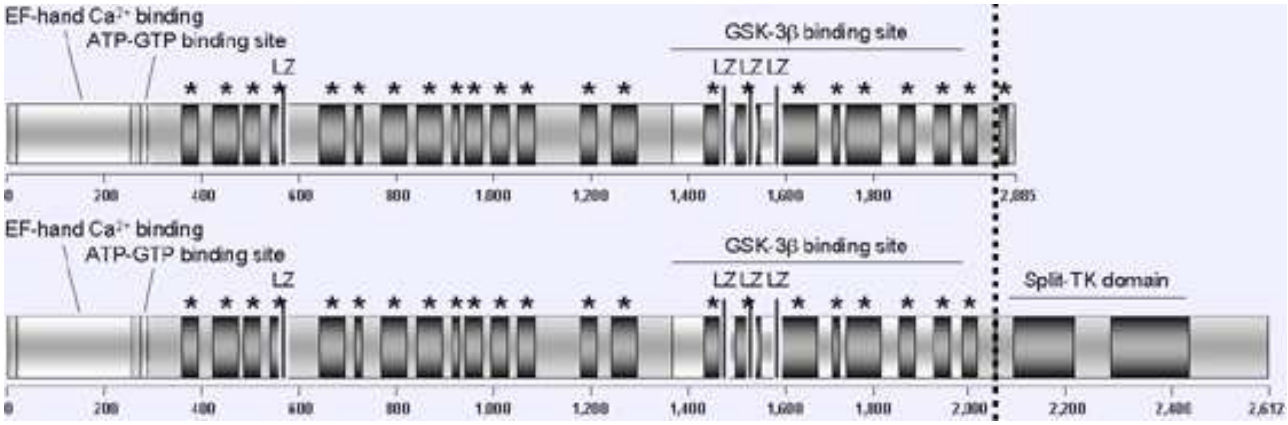
See Ref 2 below. PDGFRB-NIN was also detected.

Fusion protein

NIN-PDGFRB.jpg

Description

The fusion gene is predicted to encode a NIN-PDGFRB protein of 300 kDA (2595 aminoacids)



Schematic representation of the fusion NIN-PDGFRB consequence of the t(5;14)(q33;q24) in a chronic myeloproliferative disorder with eosinophilia. From up to down: PDGFRB, NIN and the putative chimeric NIN-PDGFRB structure. TM, transmembrane domain; TK, tyrosine kinase domain; LZ, leuzine-zipper domain. Coiled coil domains on NIN and NIN-PDGFRB are indicated with asterisks.

retaining most of NIN protein (2047 of the wild-type 2116 aminoacids) and most of the intracellular domain of PDGFRB (548 aminoacids), including the entire tyrosine kinase domain. This fusion involves PDGFRB exon 12, whereas all other reported PDGFRB fusions involve exon 11. Consequently, NIN-PDGFRB lacks the PDGFRB transmembrane domain. From ninein, the fusion would retain the potential GTP-binding site, a large coiled-coil domain, four leucine-zipper domains and a GSK-3B binding site.

Oncogenesis

NIN shares features in common with other tyrosine kinase fusion partners, namely widespread expression and the presence of putative oligomerization domains. Although there is no direct experimental proof, it is likely that the NIN promoter drives expression of the chimeric gene in hemopoietic progenitor cells, and the oligomerization domain(s) result in ligand-independent activation of the PDGFRB kinase moiety by mimicking the normal process of ligand-induced receptor dimerization.

References

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