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Short Communication

t(5;17)(q33;p13) RABEP1/PDGFRB

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Abstract

The t(5;17)(q33;p13) rearrangement has been observed as sole cytogenetic abnormality in one case of chronic myelomonocytic leukemia, a soft-tissue aneurysmal bone cyst, and a case of myeloid and lymphoid neoplasms (MLNs) with eosinophilia. Rare occurrence of lymphoid and mixed MLNs with abnormalities of PDGFRB has been reported in two cases. The t(5;17)(q33;p13) generates a fusion gene, located on the rearranged chromosome 5, comprised of the 5' portion of RABEP1 (encoding the coiled-coil domain) and the 3' portion of PDGFRB (encoding the intracellular kinase domain). Expression of the resulting fusion protein has been demonstrated to cause myeloproliferative disease in mice.

Clinics and pathology

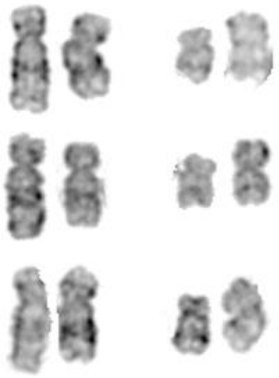
Disease

Chronic myelomonocytic leukemia (CMML) and myeloid and lymphoid neoplasm (MLN) with mixed myeloproliferative/myelodysplastic features and (T-LBL).

Note

One case of aneurysmal bone cyst with t(5;17)(q33;p13) RABEP1/PDGFRB has also been described.

Ondrejka et al., 2014 also reports a second case of MLN with eosinophilia and PDGFRB rearrangement, a 38 year old male. This patient exhibited T-LBL and an unclassifiable myeloproliferative neoplasm. A sole cytogenetic abnormality, t(5;6)(q22;q21), was observed. Molecular studies revealed a novel C6orf204-PDGFRB fusion.



t(5;17)(q33;p13) in G-banded chromosome

Phenotype/cell stem origin

Pluripotent hematopoetic stem cell in the MLN case.

Epidemiology

One case of CMML with t(5;17)(q33;p13) to date: a male patient aged 29 at diagnosis (Magnusson et al., 2001 and Magnusson et al., 2002) and one case of t(5;17)(q33;p13) in MLN with mixed features and T-LBL : male, 64 years of age at diagnosis (Ondrejka et al., 2014).

Clinics

Massive splenomegaly, anemia, mild thrombocytopenia, leukocytosis comprised primarily of neutrophils and monocytes in the CMML patient (Magnusson et al., 2001, Magnusson et al., 2002); splenomegaly and diffuse adenopathy, anemia, thrombocytopenia, mild eosinophilia in the MLN patient (Ondrejka et al., 2014).

Cytology

CMML case: hypercellular bone marrow with left shift (Magnusson et al., 2001).

Pathology

MLN case: T lymphoblasts were positive by flow cytometery for CD1a, CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD38, and CD45.
Bone marrow biopsy was hypercellular and demonstrated features of a myeloid neoplasm with mixed myeloproliferative/myelodysplastic features and no T-LBL involvement.
Marrow displayed abnormal granulocytic maturation, mild dyserythropoiesis, and atypical, small megakaryocytes (Ondrejka et al., 2014).

Treatment

CMML case: Allogeneic stem cell transplant from HLA-matched sibling (Magnusson et al., 2002). Relapsed 15 months after SCT. Received STI571 treatment and achieved molecular remission by 6 weeks, which was maintained for 6 months at time of report (Magnusson et al., 2002).
MLN case: Vincristine/prednisone-based induction. Imatinib treatment for 18 days, then ceased due to drug intolerance. Patient opted for hospice care (Ondrejka et al., 2014).

Cytogenetics

Cytogenetics morphological

Cytogenetic analysis has revealed t(5;17)(q33;p13) as a sole abnormality.

Cytogenetics molecular

Metaphase FISH analysis with PDGFRB break apart probe reveals rearrangement of 5q33, interphase FISH with probe encompassing RABEP1 locus reveals rearrangement of 17p13.

Probes

LPH031-A, CytoCell, Cambridge, UK. RP11-457I18, Blue Gnome, Cambridge, UK.

Additional anomalies

Reported only as a sole anomaly.

Variants

PDGFRB is involved in rearrangements with numerous other translocation partners.

Genes involved and proteins

PDGFRB

Location 5q33; chr5:150,113,839-150,155,859 (hg38)

DNA/RNA

Gene is 42 kb and contains 26 exons. Transcription occurs in telomere to centromere orientation. 5 transcripts are reported.

Protein

PDGRFB encodes a tyrosine kinase receptor that is located on the plasma membrane and is activated by binding of members of the platelet-derived growth factor family of proteins.
The product of the largest transcript is 1106 amino acids. Composed from NH2 to COOH of: Ig-like extracellular domains, a transmembrane domain, and a cytosolic tyrosine kinase domain.

RABEP1

Location 17p13.2; chr17: 5,282,263-5,385,812 (hg38)

DNA/RNA

Gene is 103 kb and contains 20 exons. Transcription occurs in centromere to telomere orientation. 6 transcripts are reported.

Protein

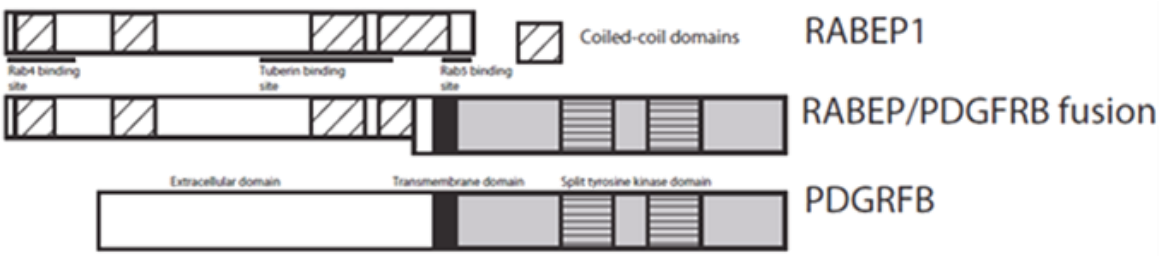
RABEP1 encodes a protein involved in endocytic membrane fusion and the trafficking of recycling endosomes.
The product of the largest transcript is 826 amino acids and contains coiled-coil domains, a NH2-terminal RAB4 binding site, and a COOH-terminal RAB5 binding site.

Result of the chromosomal anomaly

Hybrid gene

Description

5' RABEP1- 3' PDGFRb; no reciprocal transcript.



A schematic of the fusion transcript generated by the t(5;17)(q33;p13) rearrangement. Modified from Magnusson et al., 2001

Fusion protein

Description

1318 amino acid fusion protein, including the first 739 aa of RABEP1 fused to the transmembrane and cytosolic tyrosine kinase domains of PDGFRB.

Oncogenesis

Expression of the fusion protein via infection with a MSCV-based retroviral plasmid was sufficient to transform Ba/F3 cells such that they grew independent of IL-3 (Magnusson et al., 2001). Expression of the fusion gene in murine bone marrow cells transplanted into lethally irradiated mice caused development of fatal myeloproliferative disorder (Magnusson et al., 2001).

References

Magnusson MK, Meade KE, Nakamura R, Barrett J, Dunbar CE. Activity of STI571 in chronic myelomonocytic leukemia with a platelet-derived growth factor beta receptor fusion oncogene. Blood. 2002 Aug 1;100(3):1088-91

Ondrejka SL, Jegalian AG, Kim AS, Chabot-Richards DS, Giltnane J, Czuchlewski DR, Shetty S, Sekeres MA, Yenamandra A, Head D, Jagasia M, Hsi ED. PDGFRB-rearranged T-lymphoblastic leukemia/lymphoma occurring with myeloid neoplasms: the missing link supporting a stem cell origin. Haematologica. 2014 Sep;99(9):e148-51

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