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Leukaemia Section
Short Communication

inv(3)(q21q26) RPN1/MECOM / t(3;3)(q21;q26) RPN1/MECOM / ins(3;3)(q26;q21q26) RPN1/MECOM

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Abstract

Review on inv(3)(q21q26) RPN1/MECOM, with data on clinics, and the genes implicated.

Identity

Note

The three chromosome anomalies are variants of each other, and they share identical features.

Clinics and pathology

Disease

inv(3) and t(3;3) have been documented in de novo AML (in all FAB subtypes except M3), t-AML, s-AML, myelodysplastic syndrome (MDS), chronic myelogenous leukaemia (CML), more often in accelerated phase or blast crisis, and in other myeloproliferative disorders. AML with inv(3)(q21q26) or t(3;3)(q21;q26) are part of the new WHO 2008 classification in the AML subgroup with recurrent genetic abnormalities.

Phenotype/cell stem origin

Hematopoietic stem cell with multilineage potential is implicated.

Epidemiology

inv(3)(q21q26) and t(3;3)(q21;q26) are the most common 3q abnormalities in AML (32%).

The frequency of these rearrangements is estimated to range between 1.4% and 1.6% of AML in adults with no difference between sexes.

These rearrangements are slightly more common in patients aged 60 years or younger, and extremely rare in pediatric AML.

Clinics

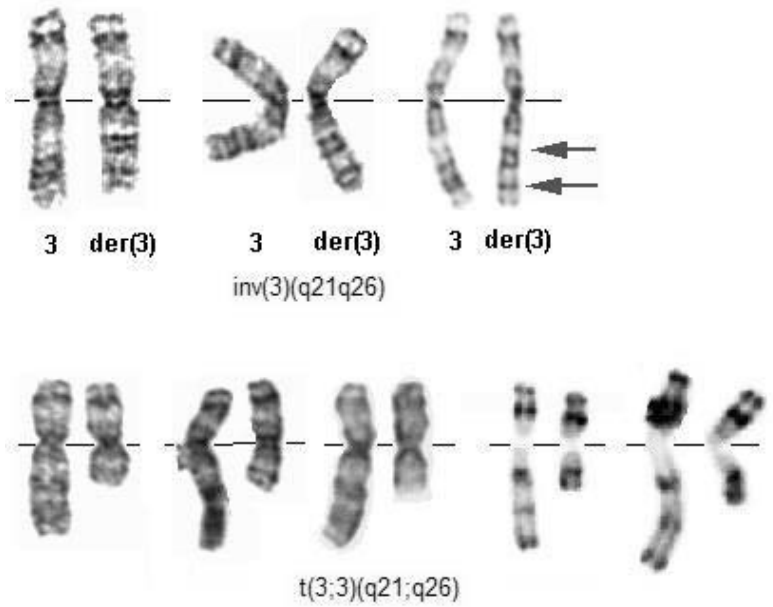
Patients may present a normal platelet count, however marked thrombocytosis may occur in 7% to 22% of patients.

Cytology

Blasts express CD13, CD33, CD117, HLA-DR, CD56, CD34 and CD38; CD7 is aberrantly expressed in some cases, whereas the other lymphoid markers are uncommon; blasts may also express megakaryocytic markers such as CD41 or CD61.

Blasts present morphologic and cytochemical features of any AML subtypes other than M3. Multilineage dysplasia is frequently associated with dysmegakaryopoiesis (characterized by small monolobate or bilobate megakaryocytes that can be increased in number).

In peripheral blood, morphological abnormalities may be observed: hypogranular neutrophil, pseudo-Pelger anomaly, macrothrombocytes, circulating micromegakaryocytes.



inv(3)(q21q26) G-banding (top) - Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap Cytogenetics at the Waisman Center (left and middle) and Jean-Luc Lai and Alain Vanderhaegen, bottom: t(3;3)q21;q26) (bottom) G-banding (left) - Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap (left and center left), Jean-Luc Lai and Alain Vanderhaegen (middle) , and R-banding (middle right and right) - Courtesy Christiane Charrin

Prognosis

Patients with inv(3)(q21q26) or t(3;3)(q21;26) present an aggressive course with short OS and poor response to conventional therapy (CR is estimated at 31%). Studies describe an unfavourable 5-year survival rate (OS: 5.7%) with a median survival of 10.3 months. OS is shorter, if additional monosomy 7 is present. There is no difference in survival between inv(3) and t(3;3).

Cytogenetics

Note

inv(3)(q21q26) are the most frequent abnormalities, ins(3;3)(q26;q21q26) are less frequent.

Additional anomalies

In AML, the most frequent additional anomaly is monosomy 7 (66% of cases), deletion 7q may occur in 3%, deletion 5q in 6%; complex karyotype is observed in 21% of cases, and monosomal karyotype in 68%. In CML, inv(3) or t(3;3) can be an additional anomaly to t(9;22)(q34;q11), but t(9;22) has also been found additional to inv(3).

Genes involved and proteins

MECOM

Location

3q26.2

Note

Alias EVI1.

DNA/RNA

EVI1 has 16 exons, and five alternative mRNA 5'-ends: EVI1-1A, EVI1-1B, EVI1-1C, EVI1-1D and EVI1-3L.

Protein

EVI1 encodes a nuclear zinc finger protein that is a transcriptional regulator involved in cell proliferation, differentiation, and apopotosis.

RPN1

Location

3q21

DNA/RNA

RPN1 has 10 exons.

Protein

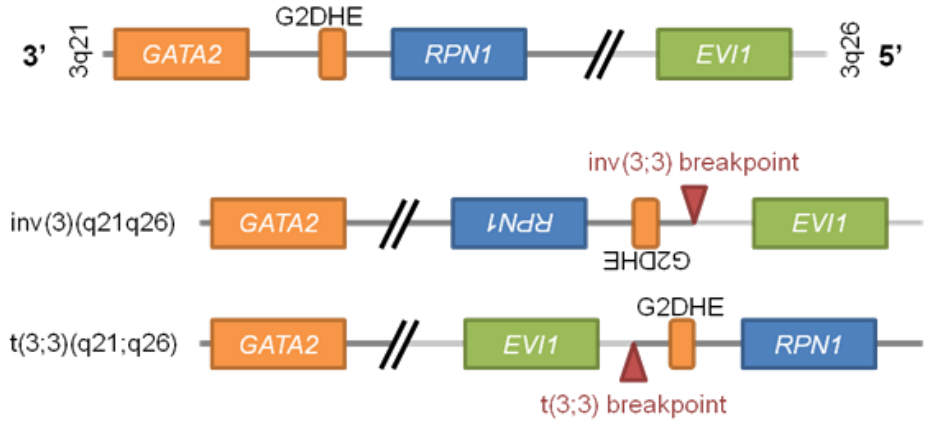
RPN1 encodes a transmembrane glycoprotein, localized in the rough endoplasmic reticulum.

Result of the chromosomal anomaly

Hybrid gene

Description

inv(3)(q21q26) or t(3;3)(q21q26) lead to a juxtaposition of the region surrounding the RPN1 gene in 3q21 with the EVI1 gene in 3q26. Breakpoints occur about 900 kb located 5' and 3' to the EVI1 gene with the t(3;3) and the inv(3) respectively. Breakpoints in the RPN1 gene area span over 235 kb and are either located 3' or centromeric to the RPN1 gene.



Boxes represent genes. Breakpoints in 3q26.2 locus are distributed on each side of EVI gene: 5' in t(3;3) and 3' in inv(3). GATA2 = GATA Binding Protein 2; G2DHE = GATA2 distal hematopoietic enhancer. Diagram is not to scale. Courtesy Thomas Smol.

Recently, studies have described a role for G2DHE, GATA2 distal hematopoietic enhancer, that is located 160 kb 3' to the RPN1 gene on 3q21. In 3q21q26 rearrangements, G2DHE is juxtaposed to EVI1 and is thought to induce EVI1 gene transcription instead of GATA2 and thus promote leukemogenesis.

To be noted

Note

AML with inv(3) or t(3;3) are associated with NRAS mutations (28%), FLT3-ITD mutations (less than 20%), and rare NPM1 mutations.

EVI1 overexpression has been described without 3q21q26 rearrangement and conversely, there are extremely rare cases of 3q21q26 rearrangement without EVI1 overexpression.

Recently, Groschel et al. have observed that 98% of myeloid malignancies with inv(3) and t(3;3) present mutations in gene activating RAS/RTK signalling pathways.

References

Aytekin M, Vinatzer U, Musteanu M, Raynaud S, Wieser R. Regulation of the expression of the oncogene EVI1 through the use of alternative mRNA 5'-ends. Gene. 2005 Aug 15;356:160-8

Balgobind BV, Lugthart S, Hollink IH, Arentsen-Peters ST, van Wering ER, de Graaf SS, Reinhardt D, Creutzig U, Kaspers GJ, de Bont ES, Stary J, Trka J, Zimmermann M, Beverloo HB, Pieters R, Delwel R, Zwaan CM, van den Heuvel-Eibrink MM. EVI1 overexpression in distinct subtypes of pediatric acute myeloid leukemia. Leukemia. 2010 May;24(5):942-9

Bobadilla D, Enriquez EL, Alvarez G, Gaytan P, Smith D, Slovak ML. An interphase fluorescence in situ hybridisation assay for the detection of 3q26.2/EVI1 rearrangements in myeloid malignancies. Br J Haematol. 2007 Mar;136(6):806-13

De Braekeleer E, Douet-Guilbert N, Basinko A, Bovo C, Guéganic N, Le Bris MJ, Morel F, De Braekeleer M. Conventional cytogenetics and breakpoint distribution by fluorescent in situ hybridization in patients with malignant hemopathies associated with inv(3)(q21;q26) and t(3;3)(q21;q26). Anticancer Res. 2011 Oct;31(10):3441-8

Fonatsch C, Gudat H, Lengfelder E, Wandt H, Silling-Engelhardt G, Ludwig WD, Thiel E, Freund M, Bodenstein H, Schwieder G. Correlation of cytogenetic findings with clinical features in 18 patients with inv(3)(q21q26) or t(3;3)(q21;q26). Leukemia. 1994 Aug;8(8):1318-26

Grigg AP, Gascoyne RD, Phillips GL, Horsman DE. Clinical, haematological and cytogenetic features in 24 patients with structural rearrangements of the Q arm of chromosome 3. Br J Haematol. 1993 Jan;83(1):158-65

Gröschel S, Sanders MA, Hoogenboezem R, Zeilemaker A, Havermans M, Erpelinck C, Bindels EM, Beverloo HB, Döhner H, Löwenberg B, Döhner K, Delwel R, Valk PJ. Mutational spectrum of myeloid malignancies with inv(3)/t(3;3) reveals a predominant involvement of RAS/RTK signaling pathways. Blood. 2015 Jan 1;125(1):133-9

Jenkins RB, Tefferi A, Solberg LA Jr, Dewald GW. Acute leukemia with abnormal thrombopoiesis and inversions of chromosome 3. Cancer Genet Cytogenet. 1989 Jun;39(2):167-79

Jotterand Bellomo M, Parlier V, Mühlematter D, Grob JP, Beris P. Three new cases of chromosome 3 rearrangement in bands q21 and q26 with abnormal thrombopoiesis bring further evidence to the existence of a 3q21q26 syndrome. Cancer Genet Cytogenet. 1992 Apr;59(2):138-60

Lugthart S, Gröschel S, Beverloo HB, Kayser S, Valk PJ, van Zelderen-Bhola SL, Jan Ossenkoppele G, Vellenga E, van den Berg-de Ruiter E, Schanz U, Verhoef G, Vandenberghe P, Ferrant A, Köhne CH, Pfreundschuh M, Horst HA, Koller E, von Lilienfeld-Toal M, Bentz M, Ganser A, Schlegelberger B, Jotterand M, Krauter J, Pabst T, Theobald M, Schlenk RF, Delwel R, Döhner K, Löwenberg B, Döhner H. Clinical, molecular, and prognostic significance of WHO type inv(3)(q21q26.2)/t(3;3)(q21;q26.2) and various other 3q abnormalities in acute myeloid leukemia. J Clin Oncol. 2010 Aug 20;28(24):3890-8

Medeiros BC, Kohrt HE, Arber DA, Bangs CD, Cherry AM, Majeti R, Kogel KE, Azar CA, Patel S, Alizadeh AA. Immunophenotypic features of acute myeloid leukemia with inv(3)(q21q26.2)/t(3;3)(q21;q26.2). Leuk Res. 2010 May;34(5):594-7

Secker-Walker LM, Mehta A, Bain B. Abnormalities of 3q21 and 3q26 in myeloid malignancy: a United Kingdom Cancer Cytogenetic Group study. Br J Haematol. 1995 Oct;91(2):490-501

Shi G, Weh HJ, Dührsen U, Zeller W, Hossfeld DK. Chromosomal abnormality inv(3)(q21q26) associated with multilineage hematopoietic progenitor cells in hematopoietic malignancies. Cancer Genet Cytogenet. 1997 Jul 1;96(1):58-63

Testoni N, Borsaru G, Martinelli G, Carboni C, Ruggeri D, Ottaviani E, Pelliconi S, Ricci P, Pastano R, Visani G, Zaccaria A, Tura S. 3q21 and 3q26 cytogenetic abnormalities in acute myeloblastic leukemia: biological and clinical features. Haematologica. 1999 Aug;84(8):690-4

Yamazaki H, Suzuki M, Otsuki A, Shimizu R, Bresnick EH, Engel JD, Yamamoto M. A remote GATA2 hematopoietic enhancer drives leukemogenesis in inv(3)(q21;q26) by activating EVI1 expression. Cancer Cell. 2014 Apr 14;25(4):415-27

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