Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

Leukaemia Section
Short Communication

i(9)(p10)

Adriana Zamecnikova

Kuwait Cancer Control Center, Kuwait annaadria@yahoo.com

Published in Atlas Database: May 2018

Online updated version : http://AtlasGeneticsOncology.org/Anomalies/i09p10ID1604.html
Printable original version : http://documents.irevues.inist.fr/bitstream/handle/2042/70480/05-2018-i09p10ID1604.pdf
DOI: 10.4267/2042/70480

Abstract

Loss of genetic material from the long arm of chromosome 9 is a common finding in patients with hematological malignancies. These deletions can result from true loss of 9q or complex rearrangements such as dicentric chromosomes, unbalanced translocations, and formation of an isochromosome of the short arm of chromosome 9. Isochromosome i(9)(p10) is an infrequent event that has been described mainly in myeloid malignancies and B-cell lymphomas.

Keywords
i(9)(p10), JAK2, 9p gain, genomic imbalance.

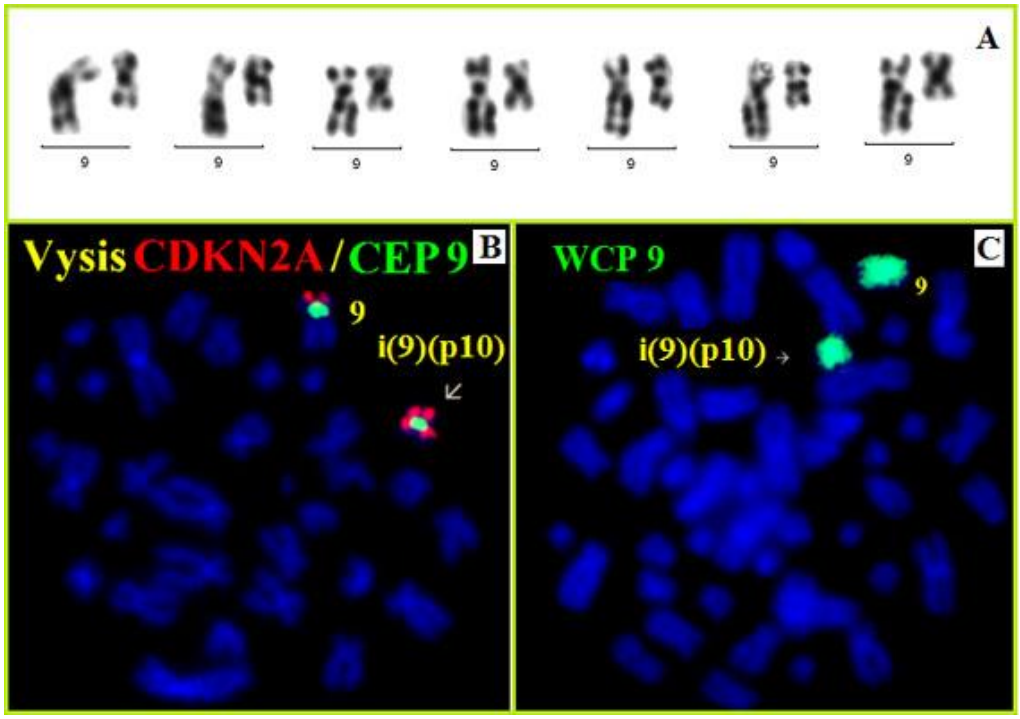

Figure 1. Partial karyotypes with i(9)(p10) (A). Fluorescence in situ hybridization with LSI CDKN2A/CEP9 probe (Vysis/Abott molecular, US) showing 3 copies of CDKN2A located on 9p (red signal) as a result of isochromosome formation (B). Hybridization with whole chromosome 9 probe (Metasystems, Germany) showing 1 normal chromosome 9 and the der(9) chromosome (green signal) (C).

Clinics and pathology

Disease

Myeloid malignancies mainly, acute lymphoblastic leukemia (ALL) and lymphomas.

Phenotype/cell stem origin

Found in chronic and acute myeloid malignancies and mainly B-cell lymphoid malignancies.

Etiology

Chronic myeloid malignancies in 12 (7M/5F aged 43 to 87 years, median 57 years): 1 chronic myeloproliferative disorder (MPD) (Hoo et al., 1987), 4 polycythemia vera (PV) (Chen et al., 1998; Najfeld et al., 2007) and 7 myelodysplastic syndrome (MDS) patients (Billstrom et al., 1988; Smadja et al., 1988; Iurlo et al., 1989; Wang et al., 1997; Lindvall et al., 2001; Stamatoullas et al., 2006; Najfeld et al., 2007). Among them, 3 patients developed MDS after chemotherapy for multiple myeloma (Smadja et al.,1988; Iurlo et al., 1989) or chronic lymphocytic leukemia (Wang et al., 1997).

Acute myeloid leukemia in 9 (4M/5F aged 13 to 79 years, median 67 years): 1 acute myeloblastic leukemia with maturation (AML-M2) (Poppe et al., 2004), 2 acute myelomonocytic leukemia (AML-M4) (Adriaansen et al., 1988; Poppe et al., 2004), 1 acute monoblastic leukemia without differentiation (AML-M5a) (Negrini et al., 1995), 1 acute megakaryoblastic leukemia (AML-M7) (Teyssier et al., 1987) and 4 acute myeloid leukemia, NOS (Pedersen et al., 1997; Van Limbergen et al., 2002; Shali et al., 2006; Moosavi et al., 2009). 1 of them developed acute myeloid leukemia 1 year after a myeloproliferative disorder was diagnosed (Negrini et al., 1995).

Acute lymphoblastic leukemia in 5 (4M/1F aged 10 and 14 years, 3 unknown); 3 patients were diagnosed with B-ALL (Heerema et al., 1992; Paulsson et al., 2015; Coyaud et al 2010) and 2 with T-ALL (Gladstone et al., 1998).

B-cell lymhoma in 13: diffuse large B-cell lymphoma (DLBCL) in 6 (3M/3F aged 18, 70, 73. 81 and 83 years, 2 unknown) (Mark et al., 1979; Mikraki et al., 1992; Ruminy et al., 2006; Chapiro et al., 2008; Bacher et al., 2011; Narayan et al., 2013), Hodgkin disease in 6 (3M/3F aged 12, 21, 25, 25 and 29 years, 1 unknown) (Tilly et al., 1991; Dohner et al., 1992; Schlegelberger et al., 1994; Cook et al., 2004) and a 62-years old male patient with extranodal marginal zone B-cell lymphoma (Van Roosbroeck et al., 2016).

T-cell lymhoma in 2: a 37- years old female diagnosed with angioimmunoblastic T-cell lymphoma (Lepretre et al., 2000) and a 78-years old female with adult T-cell lymphoma/leukemia (HTLV-1+) (Tanaka et al., 2001).

Epidemiology

41 patients; 22 males and 19 females aged 10 to 87 years; median 67 years.

Prognosis

i(9)(p10) usually occurs within a complex karyotype, in itself with poor prognosis, therefore its appearance may be associated with advanced disease and unfavourable prognosis; the clinical significance of isolated i(9)(p10) in MPD is unclear.

Genetics

Note

As an isochromosome 9p can be misinterpreted as 9q deletion, a much more common finding in hematological malignancies, fluorescence in situ hybridization with locus specific probes of chromosome 9p/9q is a helpful method to confirm this less frequent abnormality.

Cytogenetics

Note

Similar to i(5)(p10), described mainly in MDS and AML, two types of i(9)(p10) are observed: i(9)(p10) resulting in a loss of the long arm of the chromosome 9 (9q- and 9p trisomy) or it may be present as an extra +i(9)(p10), in addition to 2 normal chromosomes 9.

Cytogenetics morphological

Present as a supernumerary +i(9)(p10), in addition to two normal chromosomal 9 in 23 patients: 1 MPD (Hoo et al., 1987), 3 PV (Chen et al., 1998; Najfeld et al., 2007), 5 MDS (Billstrom et al., 1988; Smadja et al., 1988; Lindvall et al., 2001; Stamatoullas et al., 2006; Najfeld et al., 2007), 3 AML (Teyssier et al., 1987; Pedersen et al 1997; Van Limbergen et al., 2002), 1 ALL (Coyaud et al., 2010) and 10 B-cell lymphomas (Tilly et al., 1991; Dohner et al., 1992; Mikraki et al., 1992; Schlegelberger et al., 1994; Cook et al., 2004; Ruminy et al., 2006; Chapiro et al., 2008; Bacher et al., 2011; Narayan et al., 2013; Van Roosbroeck et al., 2016).

Additional anomalies

Found as the sole extra i(9)(p10) in 1 MPD (Hoo et al., 1987) and 3 PV patients (Chen et al., 1998; Najfeld et al., 2007), in association with i(9)(q10) in 1 PV (Najfeld et al., 2007) and 1 ALL (Heerema et al., 1992). Associated with chromosome 5/chromosome 7 anomalies or their combination in 5 MDS (Iurlo et al., 1989; Wang et al., 1997; Lindvall et al., 2001; Stamatoullas et al., 2006; Najfeld et al., 2007) and 6 AML (Teyssier et al., 1987; Pedersen et al., 1997; Van Limbergen et al., 2002; Poppe et al., 2004; Shali et al., 2006; Moosavi et al., 2009) and found with t(9;11)(p21;q23) in 2

AML patients (Cuneo et al., 1993; Negrini et al., 1995). Found with del(6q), del(7q) in 1, del(5q),del(6q) in 1 (Gladstone et al., 1998) and t(6;14)(p22;q32),+del(7q) in 1 ALL (Coyaud et al 2010). Part of complex karyotypes associated with 14q32 rearrangements in DLBCL and part of hypedriploid/near triploid complex karyotypes in Hodgkin disease patients.

Result of the chromosomal anomaly

Fusion protein

Oncogenesis

Isochromosome i(9)(p10) represents a rare but recurrent chromosome abnormality in hematological malignancies, especially in chronic myeloid disorders, acute myeloid leukemia and B-cell lymphomas such as DLBCL and Hodgkin disease. The formation of i(9)(p10) induce a loss of the long arm of the chromosome 9 and duplication of its short arm, or less frequently it results only in an extra copy of 9p when 2 normal chromosomes 9 are present. In both cases, gain of chromosome material from 9p leading to extra copies of a gene or genes appears to be important in disease pathogenesis via gene dosage effect. Among them, the tyrosine kinase gene JAK2 on 9p24.1 might be a candidate gene as its numerical gain and structural rearrangements characterize both myeloid and B-lymphoid neoplasms. Gain and amplification of chromosomal sequences spanning JAK2 has been observed in both JAK2617V>F-positive and -negative patients with Philadelphia chromosome negative myeloproliferative disorders, with or without +9/+9p chromosomal abnormalities, indicating that amplification of a genes on 9p, and not deletion of genes from 9q, may play a role in the pathogenesis (Najfeld et al., 2007). JAK2 copy gain is also one of the most common genetic alterations in B-lymphoid neoplasms, especially Hodgkin lymphoma and primary mediastinal large B-cell lymphoma (Van Roosbroeck et al., 2016). Several of the imbalances described, including a recurrent 9p24.1 amplicon that includes JAK2 and immunoregulatory PD-1 ligand genes, leading to increased JAK2 protein expression activating the JAK2/STAT signaling pathway in a copy number-dependent manner.

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This article should be referenced as such:

Zamecnikova A. i(9)(p10). Atlas Genet Cytogenet Oncol Haematol. 2019; 23(8):224-227.