

Leukaemia Section

Review

t(1;1)(p36;q21) in non Hodgkin lymphoma

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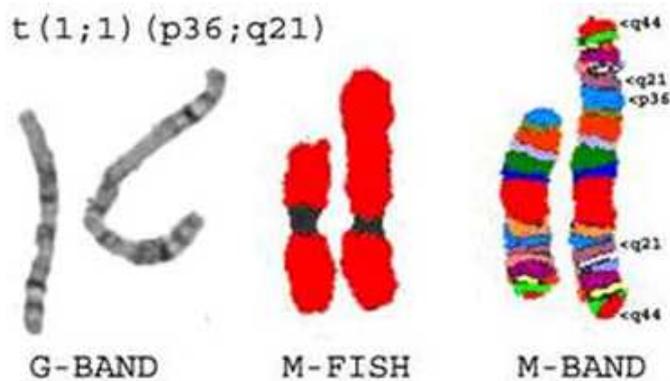
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Identity



Unbalanced t(1;1)(p36;q21) in NHL with dup(q21q44) as observed by, G-band, M-FISH and M-BAND [ISCN2005: der(1)t(p36.3;q21.1-2)dup(1)(q21.1-2q44)].

Clinics and pathology

Disease

Non Hodgkin Lymphoma (NHL). Aberrations of chromosomal bands 1p36 and 1q11-q23 are among the most common chromosomal alterations in NHL.

Phenotype / cell stem origin

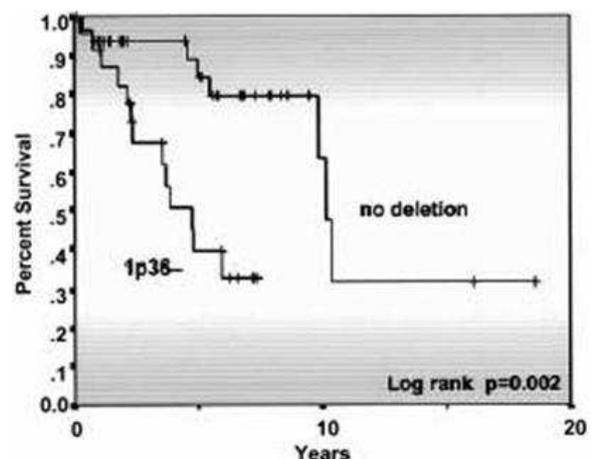
Lymphocytes (B-cell and T-cell).

Etiology

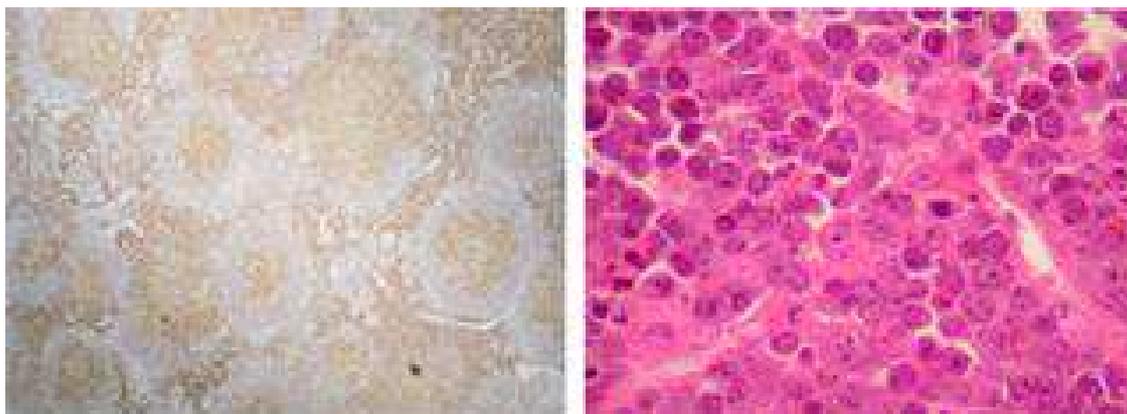
The exact etiology of NHL is still unknown, risk increases with exposed to ionizing radiation, chemicals such as pesticides or solvents, Epstein-Barr Virus infection, family history of NHL (although no hereditary pattern has been established, Human Immunodeficiency Virus (HIV) infection, immunosuppression or immunodeficiency, genetics.

Epidemiology

NHL is the 5th most frequently diagnosed cancer overall for both males and females, males are slightly more often affected than females, increasing over time.



Univariate analyses using the Kaplan-Meier method for 1p36-, demonstrating the significance of this chromosomal change for overall survival. In multivariate analysis using the Cox regression model controlling for IPI, the significance remained intact.



Transformed follicular lymphoma (courtesy, Dr. R.D. Gascoyne, BC Cancer Agency, Vancouver, Canada).

Clinics

At diagnosis, painful swelling of lymph nodes located in the neck, underarm and groin, unexplained fever, night sweats, constant fatigue, unexplained weight loss, itchy skin.

Cytology

Anti-B-cell antibodies (e.g. CD19, CD20, CD10, CD23); anti-T-cell antibodies (e.g. CD3, CD4, CD2/HLADR); other antibodies (e.g. CD45 for total lymphocytes, CD10 for monocytes).

Pathology

t(1;1)(p36;q21) has been seen in following NHL types as characterized by pathology; follicular lymphoma (FL) grades 1-3; diffuse large B-cell lymphoma; T-cell lymphoma and peripheral T-cell lymphoma.

Treatment

Depend on the stage and type and genetics of NHL; 'watch-and-wait' approach in case of indolent follicular lymphomas; radiotherapy to site of problem; systemic chemotherapy; oral agents; IV agents; antibody against CD20; stem cell or bone marrow transplant.

Evolution

Initial genomic aberration (such as t(14;18)(q32;q21) in follicular lymphoma) may or may not be sufficient for the initiation of the malignant phenotype. Additional genomic rearrangements are required for disease progression.

Prognosis

Depend on the stage, type and genetics of NHL; in general, highly treatable and some times curable. However, a number of karyotype parameters have been reported to influence prognosis in NHL. It has been demonstrated that the cytogenetic abnormality 1p36-, as a result of t(1;1)(p36;q21) or another rearrangement involving chromosome 1, was found to be a significant predictors of adverse overall survival for FL (univariate and multivariate analysis).

Genetics

Note: Initial cytogenetic changes often seen in e.g. FL and t(14;18)(q32;q21) (IGH/ BCL2); DLBL and t(3;14)(q27;q21) (BCL6 /IGH). Additional acquired mutations are necessary to generate a fully malignant clonal proliferation. Many of these secondary genetic alterations (including chromosome 1) are visible in the clonal karyotype; it is now possible to identify the sequence by which they arise and their influence on clinical behavior by using computational methods to manipulate complex chromosomal data in large number of cases.

Cytogenetics

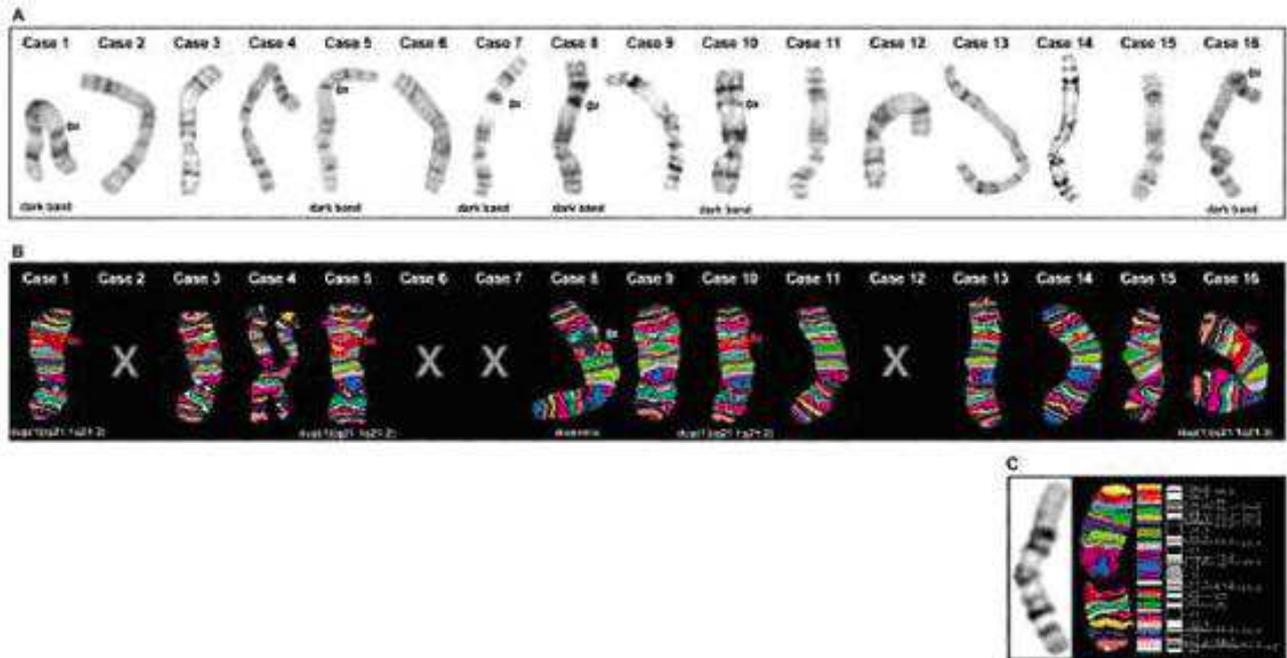
Note: t(1;1)(p36;q21). G-band and M-BAND1 Detection of der(1)t(1;1).

Cytogenetics morphological

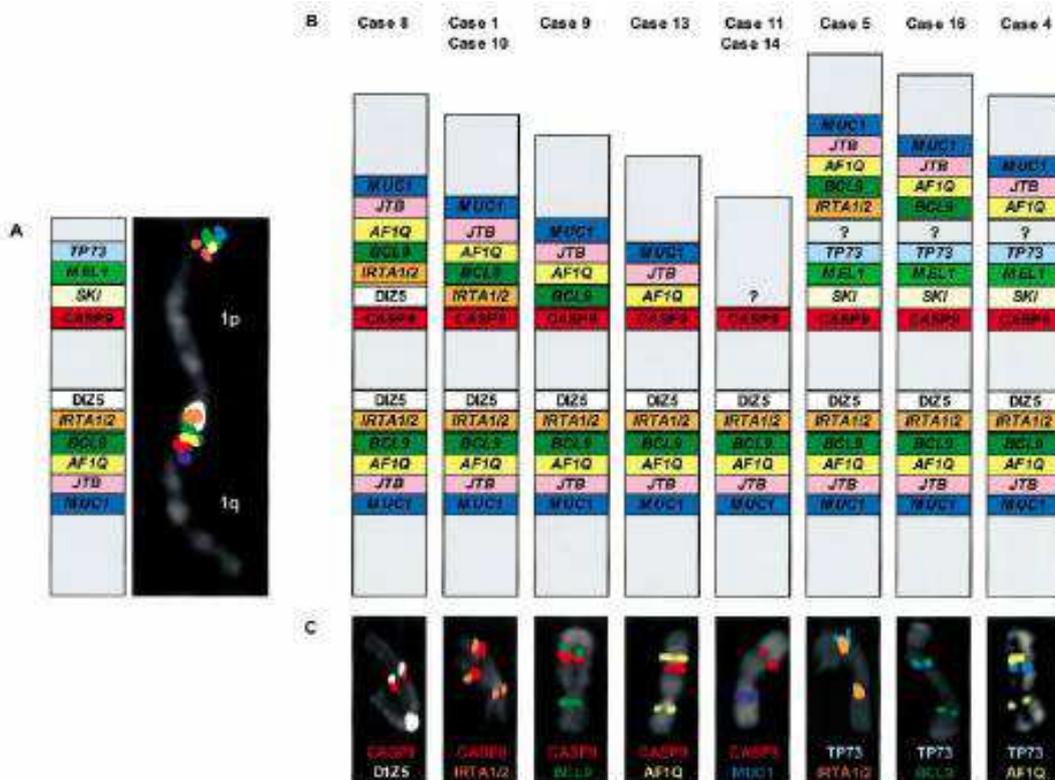
Normal chromosome 1 with derivative chromosomes 1; Breakpoints are at chromosomal positions 1p36.3 and 1q21.1-2; duplication of the 1q21 to 1q44; adverse prognosis (?as a result of 1p36 suppressor genes deletions and/or duplication of 1q21q44 oncogenes); additional secondary abnormalities to t(1;1) of various complexity as usually seen in NHL.

Cytogenetics molecular

LS-FISH identification of 1p36.3 and 1q21.1-2 breakpoints on der(1)t(1;1); Two distinct types of 1p36.3 rearrangements were observed: One type involved deletions of SKI, MEL1, and TP73, and retained CASP9 the other type showed breakpoints telomeric to TP73; Four distinct types of 1q21.1-2 rearrangements were observed: The first type involved breakpoints at IRTA1 and IRTA2 with duplications of IRTA1, IRTA2, BCL9, AF1Q, JTB, and MUC1; the second type involved a breakpoint at BCL9 with duplications of BCL9, AF1Q, JTB, and MUC1; the third type involved a breakpoint at AF1Q with duplications of AF1Q, JTB, and MUC1; the fourth type involved an undefined breakpoint telomeric to MUC1.



A: The derivative chromosome 1 in all 16 NHL cases as seen by G-band analysis. Arrows indicate the additional unidentified dark band. B: The corresponding derivative chromosome 1 as seen by M-BAND1 analysis. Arrows indicate the dup(1)(q21.1q21.2) at the p/q-arm interface (broad orange/ pink bands). X indicates cases where no material was available for M-BAND1 analysis. C: Normal chromosome 1 as seen by G-band and M-BAND1 analysis, color classifier, and ISCN 550-band level ideogram.



Composite picture of all LS-FISH patterns observed in this study with representative examples. A: Normal color-coded chromosome 1 LS-FISH pattern, demonstrating the relative localization of all BAC probes. B: All der(1)t(1;1) combinations seen by LS-FISH. C: Two color-coded representative images corresponding to B and demonstrating the p/q-arm breakpoint interfaces.

Probes

For genes MEL1, TP73, SKI, and CASP9 at 1p36; genes IRTA1, IRTA2, BCL9, AF1Q, JTB, and MUC1 at 1q21 and the =E1-satellite DNA probe for chromosome 1 (D1Z5, VYSIS).

Genes involved and Proteins

Note: The remarkable frequency of centromeric/pericentromeric rearrangements of chromosome 1 in B-cell malignancies has been clearly associated with tumor progression. A factor in the pathology associated with the centromeric/pericentromeric region 1q10-12 is a sequence-specific DNA-binding protein called Ikaros that is speculated to be essential for lymphocyte development. Methylation, interactions with proteins interfering with heterochromatin, and possible gene silencing attributed to heterochromatin may be responsible as well. The mechanisms, however, underlying the formation of recurring chromosome 1 aberrations in many hematological malignancies and the consequences of these various chromosomal rearrangements are largely undetermined.

Conserved Homology for 1p36 and 1q21?

It has been speculated that 1q21, 1p11-12, and 1p36 are evolutionarily conserved and that the homology between these regions is associated with chromosomal instability. A mechanism of homologous recombination may be in place that would explain the frequent chromosome 1 rearrangements involving 1p36, 1p11-12, and 1q21, but wouldn't explain the various breakpoints seen in these regions.

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