

Leukaemia Section

Mini Review

3q27 rearrangements in non Hodgkin lymphoma, t(3;Var)(q27;Var) in non Hodgkin lymphoma

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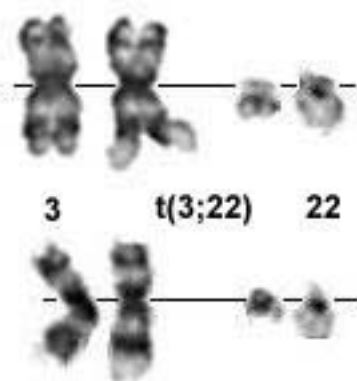
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Identity

Note

3q27 rearrangements occur in distinct clinicopathological entities of B-cell non Hodgkin lymphoma (NHL), including diffuse large cell lymphoma (DLCL), follicle centre cell lymphoma (FCCL) and marginal zone B-cell lymphoma (MZBCL) in the REAL classification; very rare cases were also reported with mantle cell lymphoma and chronic lymphocytic leukemia.

3q27 breaks are usually, but not invariably, associated with rearrangements of the BCL6 gene located at the 3q27 chromosome band; likewise rearrangements of this gene may occur without detectable 3q27 breaks.



t(3;22)(q27;q11) - Courtesy Diane H. Norback, Eric B. Johnson, Sara Morrison-Delap Cytogenetics at theWaisman Center.

Clinics and pathology

Disease

Diffuse large cell lymphoma (DLCL)

Note

This biologically heterogeneous group of lymphomas in the REAL proposal accounts for as many as 40% of NHL in western countries and includes the entities of centroblastic lymphoma, immunoblastic lymphoma and B-cell anaplastic lymphoma recognized by the Kiel classification.

Phenotype/cell stem origin

The cell of origin is probably a large transformed B-cell, frequently deriving from the follicle centre, harbouring somatic hypermutation of the Ig genes and ongoing mutations (antigen driven stimulation). The phenotype is usually CD19+, CD22+, CD10-/+, SIg+.

Epidemiology

10-20% of DLCL carry 3q27 translocations detectable at banding analysis, approximately 50% of which may be expected to be associated with BCL6 rearrangement; molecular genetic methods proved very efficient in demonstrating this genetic lesion and studies using southern blotting detecting BCL6 breaks in the 4.0 kb major breakpoint region showed 20-30% of unselected DLCL to be rearranged.

Pathology

There is no distinctive histological features in DLCL with 3q27/BCL6 rearrangement as compared with other

DLCL; the proliferation consists of a diffuse infiltrate of large cells with vesicular nuclei and prominent nucleoli with basophilic cytoplasm; criteria for distinguishing those cases with a predominance of immunoblasts or of anaplastic B-cells were put forward but were felt not to be enough reproducible as to allow for proper categorization of distinct pathological entities; 3q27 abnormalities were seen in similar frequency in the immunoblastic variant and in the centroblastic variant of DLCL in a study.

Prognosis

A predominance of extra-nodal forms and a relatively favourable outcome was observed in BCL6-rearranged DLCL but BCL6 failed as a prognostic indicator when compared to other molecular genetic lesions; thus, the assessment of the prognostic significance of 3q27 or BCL6 breaks in DLCL needs further investigation in prospective studies.

Disease

Follicle centre cell lymphoma (FCCL)

Note

FCCL accounts for approximately 30-40% of all NHL in western countries.

Phenotype/cell stem origin

The neoplasia derives from centrocytes / centroblasts unable to progress through the germinal centre, carrying somatic hypermutation of the IgV genes and a pan-B+, CD10+/-, CD5-, sIg+ phenotype.

Epidemiology

3q27 translocations involving the chromosome regions where Ig genes are located (2p11: IgK, 14q32: IgH, 22q11: IgL) were detected in 6.5% of FCCL; a 16% incidence for any 3q27 break was reported; the association of 3q27/BCL6 involvement with the classical t(14;18) was described; molecular genetic studies found a 6-14% incidence for BCL6 rearrangement in FCCL.

Prognosis

No specific correlation was established between 3q27 breaks and specific clinicopathological features of FCCL.

Disease

Marginal zone B-cell lymphoma (MZBCL)

Note

7-8% of NHL show the clinicopathological features of MZBCL.

Phenotype/cell stem origin

The transformed cells derive from marginal zone lymphocytes harbouring hypermutated IgV genes with the following phenotype: pan-B+, CD5-/+ , CD10-, CD23-, CD11c+/-, cyIg +(40% of the cells), sIgM+ bright, sIgD-.

Epidemiology

A minority of MZBCL may carry a 3q27/BCL6 translocation, mostly t(3;14)(q27;q32).

Clinics

There is no distinctive clinicopathological feature in this cytogenetic subset of MZBCL, but a predominance of extra-nodal forms over splenic and nodal types and an excess of large blast-like cells were noted.

Genetics

Note

Below are listed translocations involving -or likely to involve- BCL6 in 3q27, and a partner gene in the other breakpoint.

Cytogenetics

Cytogenetics morphological

t(2;3)(p12;q27): the gene in 2p12 is IgK.

t(3;3)(q27;q29): the gene in 3q29 is TFRC, the transferrin receptor.

t(3;4)(q27;p13): the gene in 4p13 is RHOH, a GTPase of the Ras superfamily; role in signal transduction.

t(3;6)(q27;p22): the gene in 6p22 is histone H1F1, an architectural protein with a role in chromatin condensation and in gene regulation.

t(3;6)(q27;p21.2): the gene in 6p21.2 is PIM-1, a protein kinase.

t(3;7)(q27;p12): the gene in 7p12 is ZNFN1A1/Ikaros, a Zn finger protein involved in cell differentiation.

t(3;8)(q27;q24)

t(3;11)(q27;q23): the gene in 11q23 is OBF1, a B-cell specific transcriptional coactivator.

t(3;13)(q27;q14): the gene in 13q14 is LCP1/L-plastin, a gene which belongs to an actin-binding protein family.

t(3;14)(q27;q32): the gene in 14q32 is IgH.

t(3;15)(q27;q22).

t(3;16)(q27;p13): the gene in 16p13 is MHC2TA/CIITA, a Class II histocompatibility complex transactivator.

t(3;17)(q27;q11).

t(3;18)(q27;p11.2): the gene in 18p11.2 is EIF4A2, a DEAD box helicase.

t(3;22)(q27;q11): the gene in 22q11 is IgL.

t(3;?)(q27;?): the gene is HSP89A, a member of the HSP90 sub-family of the heat-shock protein (HSP) family.

Finally, breakpoints in 1p34, 1p32, 2q21, 3p14, 6q23, 12p13, 14q11, 16p11.2, and 16p13 have also been described.

However, cases of apparently simple translocations involving 3q27 -but not 14q32- (e.g. t(1;3)(q21;q37), or t((3;6)(q27;p25)) have disclosed insertion of IgH sequences within the 3q27 breakpoint.

Moreover, in a substantial percentage of cases, a breakpoint in 3q27 in NHL is accompanied with germline BCL6: another gene is likely to be implicated in these cases (or else, the rearranged sequence, although distant, still disregulates BCL6).

Cytogenetics molecular

3q27 anomalies are often associated with well known primary anomalies such as t(8;14)(q24;q32), t(11;14)(q13;q32), t(14,18)(q32;q21).

Genes involved and proteins

BCL6

Location

3q27

Note

BCL6 mutations are regarded as a genetic marker of B-cell transition through the germinal center.

DNA/RNA

10 exons; alternative splicing of exons 1 (1a and 1b), without modification of the open reading frame.

Protein

Transcription factor; belongs to the Krüppel family, with a N-term BTB/POZ domain and 6 zinc fingers; transcription repressor.

Result of the chromosomal anomaly

Hybrid gene

Note

The translocation partners of BCL6 are not confined to the immunoglobulin superfamily, contrarily to the situation found with c-MYC, BCL1, or BCL2.

Description

Breakpoint in the first non-coding exon (containing the 2 promoters) or the first intron of BCL6; the partner gene therefore fuses with the second exon of BCL6, resulting in a 5' partner - 3' BCL6 fusion transcript; it is supposed that substitution of the promoter of BCL6 may be responsible for BCL6 regulation, or that a break in the breakpoint cluster region of BCL6 may inhibit a sequence involved in BCL6 regulation; partners other than immunoglobulin lack homology with switch regions, VDJ sequences, or Chi sequences.

Fusion protein

Description

No fusion protein; the 5' regulatory region of BCL6 is replaced by the 5' regulatory region of the partner gene.

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