Chromosome Translocations in Hematologic Malignancies

Educational Background

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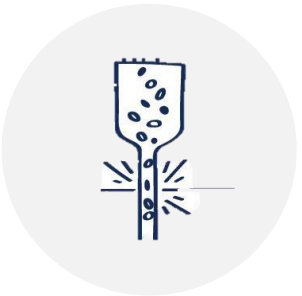
Importance of Translocation Testing

Routine Tests

Complete Blood Count
Peripheral Smear

Immuno-
histochemistry



Flow Cytometry

Confirmatory Tests

Molecular Testing

Translocation Assays

Molecular identification of markers associated with specific diseases

Translocations

Detection and assessment of translocations can provide important insights to aid in patient stratification and prognostication

Translocation	Associated Diseases
BCL1/JH	Mantle Cell Lymphoma, Multiple Myeloma other Plasma Cell Neoplasms
BCL2/JH	Follicular Lymphoma, Diffuse large B-Cell Lymphoma
***BCL2/JH* t(14;18)**	Follicular Lymphoma, Diffuse large B-Cell Lymphoma
***BCR/ABL* t(9;22)**	Chronic Myeloid Leukemia, Acute Lymphoblastic Leukemia and Myeloproliferative Neoplasms
***PML/RARa* t(15;17)**	Acute Promyelocytic Leukemia

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BCL1/JH Translocation

BCL1/JH Translocation

This gene translocation juxtaposes genes of the ***IGH* joining** (JH) region on chromosome 14q32 with the **cyclin D1 gene** on chromosome 11q13[1]

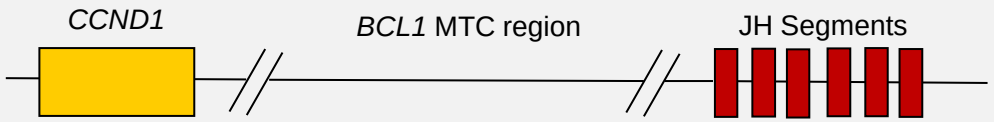
Target Background:

- Identify *BLC1/JH* gene Translocations highly suggestive of **Mantle Cell Lymphoma** (MCL, 50-70%),t(11;14)(q13:q32)[2]
- Also seen in:
  - **B-prolymphocytic leukemia** (B-PLL) (10-20%),
  - **Plasma cell leukemia** (PCL),
  - **Splenic lymphoma with villous lymphocytes** (SLVL)
  - **Chronic lymphocytic leukemia** (CLL) (2-5%), and in
  - **Multiple myeloma** (MM) (20-25%)[2]
- Distinguish MCL from other neoplastic or benign B-cell proliferations
- Monitor and evaluate disease recurrence

[1] De Boer, CJ et al. Cyclin D1 messenger RNA overexpression as a marker for mantle cell lymphoma. Oncogene 1995, 10:1833-1840
[2] Huret, JL. t(11;14)(q13;q32). Atlas Genet. Cytogenet. Oncol. Haematol. May 1998

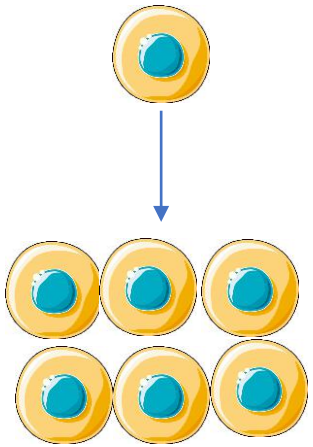
BCL1/JH Translocation

BCL1/IgH Fusion Gene



IgH enhancer stimulates the expression of Cyclin D1

Increased expression of Cyclin D1



Cyclin D1 is a regulator of the cell cycle progression

Acceleration of cell cycle progression

BCL1/JH Translocation

Related Publications:

- Rimokh et al. 1994: Detection of the Chromosomal Translocation t(11;14) by Polymerase Chain Reaction in Mantle Cell Lymphomas

Why you should read it

- PCR as a reliable tool for t(11;14)(q13;q32) detection

Detection of the Chromosomal Translocation t(11;14) by Polymerase Chain Reaction in Mantle Cell Lymphomas

By Ruth Rimokh, Françoise Berger, Georges Delsol, Isabelle Digonnet, Jean Pierre Rouault, Jean Dominique Tigaud, Mylène Gadoux, Bertrand Coiffier, Paul André Bryon, and Jean Pierre Magaud

The t(11;14)(q13;q32) and its molecular counterpart, *BCL1* rearrangement, are consistent features of mantle cell lymphoma (MCL). Rearrangement is thought to deregulate the nearby *CCND1* (*BCL1/PRAD1*) proto-oncogene, a member of the cyclin G_1 gene family, and thereby to contribute to tumorogenesis. We and others have previously shown that the *BCL1* locus is rearranged in 55% to 60% of MCL patients and that, on chromosome 11, more than 80% of the breakpoints are localized within a 1-kbp DNA segment known as the major translocation cluster (MTC). We have determined the nucleotide sequence for a portion of the MTC region, and constructed chromosome 11-specific oligonucleotides that were in conjunction with a consensus immunoglobulin (Ig) heavy chain joining region (JH) primer used to perform the polymerase chain reaction (PCR) to amplify t(11;14) chromosomal junctional sequences in DNA from 16 MCL patients with breakpoints in the MTC region. 15 of the 16 breakpoints that occurred at the MTC region were amenable to PCR detection. The sizes of the amplified bands, the existence or not of a *Sac* I site in the PCR products, and nucleotide sequencing of the amplified DNA from four patients showed that the breakpoints share a remarkable tendency to tightly cluster within 300 bp on chromosome 11, some of them occurring at the same nucleotide. On chromosome 14, the breakpoints were localized within the Ig JH. Our findings indicate that a *BCL1* rearrangement can be detected using this approach in roughly one half of the MCL patients. This has implications for both the diagnosis and the clinical management of MCL.

BCL1/JH Translocation

Related Publications:

- De Boer et al. 1995: Cyclin D1 messenger RNA overexpression as a marker for mantle cell lymphoma

Why you should read it

- t(11;14)(q13;q32) chromosomal rearrangement and overexpression of cyclin D1 as a reliable marker for the classification mantle cell lymphoma

Oncogene. 1995 May 4;10(9):1833-40.

Cyclin D1 messenger RNA overexpression as a marker for mantle cell lymphoma.

de Boer CJ[1], van Krieken JH, Kluin-Nelemans HC, Kluin PM, Schuuring E.

⊕ Author information

Abstract

In mantle cell lymphoma (MCL) a recurrent chromosomal rearrangement, t(11;14)(q13;q32), has been described. Most breakpoints have been detected within the 120 kb BCL-1 region, upstream of the cyclin D1 gene. To evaluate the association between BCL-1 rearrangement and expression of cyclin D1 in lymphoproliferative disorders, we analysed a series of 24 MCL, 56 other B-cell non-Hodgkin's lymphomas (NHL), 28 chronic B-cell leukemias, 18 hematopoietic cell lines and 10 normal lymphoid tissues at the RNA level. Hematopoietic cell lines with a known 11q13 translocation showed high expression of the 4.5 kb cyclin D1 transcript. Three B-cell lines without known 11q13 breakpoint showed low expression. We detected high expression in all (11/11) MCL with and in 11 out of 13 cases of MCL without detectable t(11;14) rearrangement. In three cases with a rearrangement at the 3' end of cyclin D1, two showed overexpression of the 1.5 kb transcript and one expression of an aberrant (3.0 kb) transcript. In other lymphoproliferative disorders, only 5/15 hairy cell leukemias, all without detectable t(11;14), and 5/8 B-cell leukemias suspected to be MCL in leukemic phase showed expression levels comparable to MCL, whereas no or only low expression were observed in 56 cases of other NHL, seven chronic B-cell leukemias and all (10/10) normal lymphoid tissues. Cell sorting experiments on fresh tonsils showed that this low expression was present in normal B-cells and not in T-cells. In contrast to other studies, our data indicate that cyclin D1 is expressed in many lymphoproliferative disorders and normal tissues, albeit at low levels. High levels of expression of cyclin D1 however is restricted to MCL and some hairy cell leukemias. We therefore propose that overexpression of cyclin D1 is a reliable marker for the classification of MCL.

PMID: 7753558

[Indexed for MEDLINE]

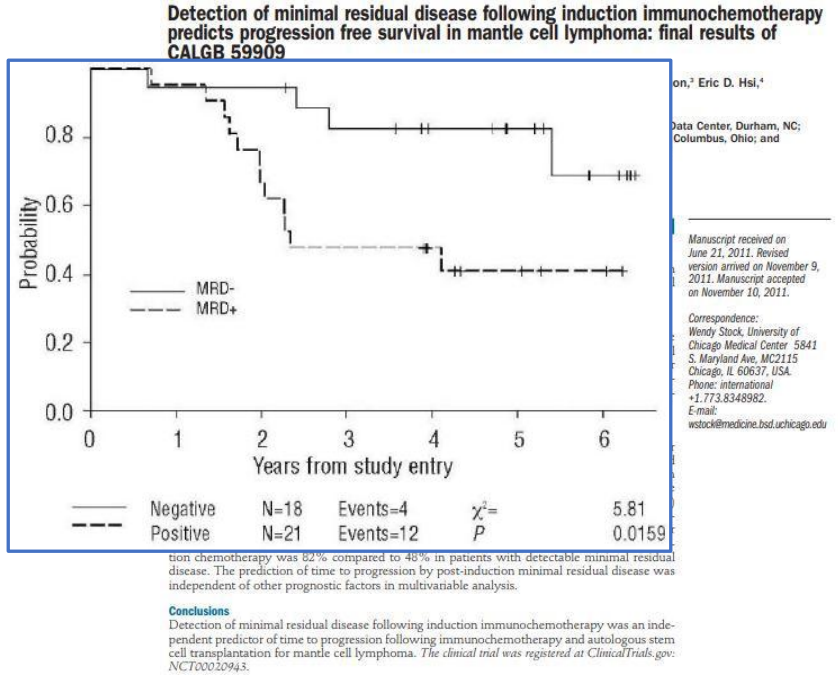
BCL1/JH Translocation

Related Publications:

- Liu H et al. 2011: Detection minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: final results of CALGB 59909

Why you should read it

- IVS *BCL1/JH* assay used for MRD detection
- MRD detection following induction therapy used for predicted disease progression prediction



Detection of minimal residual disease following induction immunochemotherapy predicts progression free survival in mantle cell lymphoma: final results of CALGB 59909

on,[3] Eric D. Hsi,[4]

Data Center, Durham, NC; Columbus, Ohio; and

Manuscript received on June 21, 2011. Revised version arrived on November 9, 2011. Manuscript accepted on November 10, 2011.

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tion chemotherapy was 82% compared to 48% in patients with detectable minimal residual disease. The prediction of time to progression by post-induction minimal residual disease was independent of other prognostic factors in multivariable analysis.

Conclusions

Detection of minimal residual disease following induction immunochemotherapy was an independent predictor of time to progression following immunochemotherapy and autologous stem cell transplantation for mantle cell lymphoma. *The clinical trial was registered at ClinicalTrials.gov: NCT00020943.*

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BCL2/JH Translocation

BCL2/JH Translocation

BCL2 translocations are reciprocal chromosome exchanges that place the *bcl-2* proto-oncogene under transcriptional control of the *IGH* gene.

Target Background:

- Distinguish **Follicular Cell Lymphoma (FL, 70-90%)** from other B-cell lymphomas that may have a similar appearance
- Distinguish lymphoma from benign lymphoid hyperplasia
- The *BCL2/JH* translocation leads to increased expression of the **BCL2 protein** which is an antagonist to apoptosis and therefore increased level of B-cells in the body
- Monitor and evaluate disease recurrence
- The majority of breakpoints on 18q21-22 occur within the major breakpoint region (Mbr) (60-70% of the cases), and the minor cluster region (mcr) (20-25% of the cases)

Van Dongen, JJM *et al*. Design and standardization of PCR primers and protocols for detection of clonal immunoglobulin and T-cell receptor gene recombinations in suspect lymphoproliferations: Report of the BIOMED-2 Concerted Action BMH4-CT98-3936. *Leukemia*. 2003, **17(12)**:2257-2317

BCL2/JH Translocation

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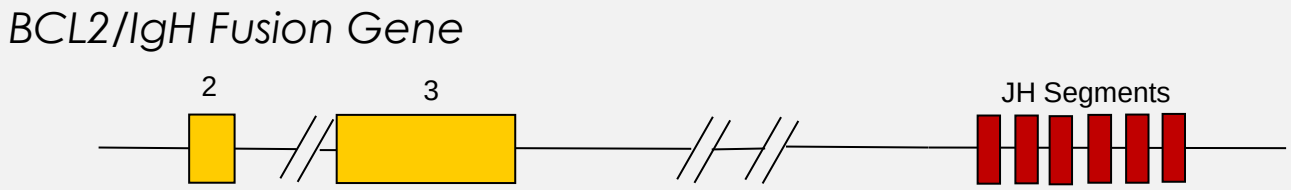
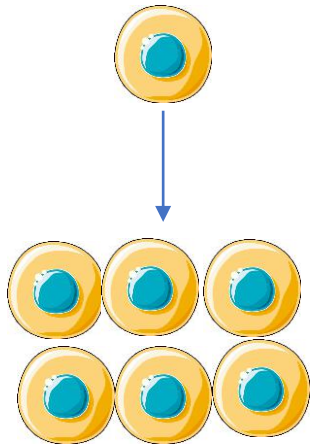
Chiu, C.-H. et al. The Utility of t(14;18) in Understanding Risk Factors for Non-Hodgkin Lymphoma Brian. J Natl Cancer Inst Monogr 2008;39:69–73

BCL2/JH Translocation



BCL2 gene under aberrant transcriptional control of IGH gene

Increased expression of Bcl-2 protein



Bcl-2 protein is an antagonist to apoptosis

Increased level of B-cells in the body

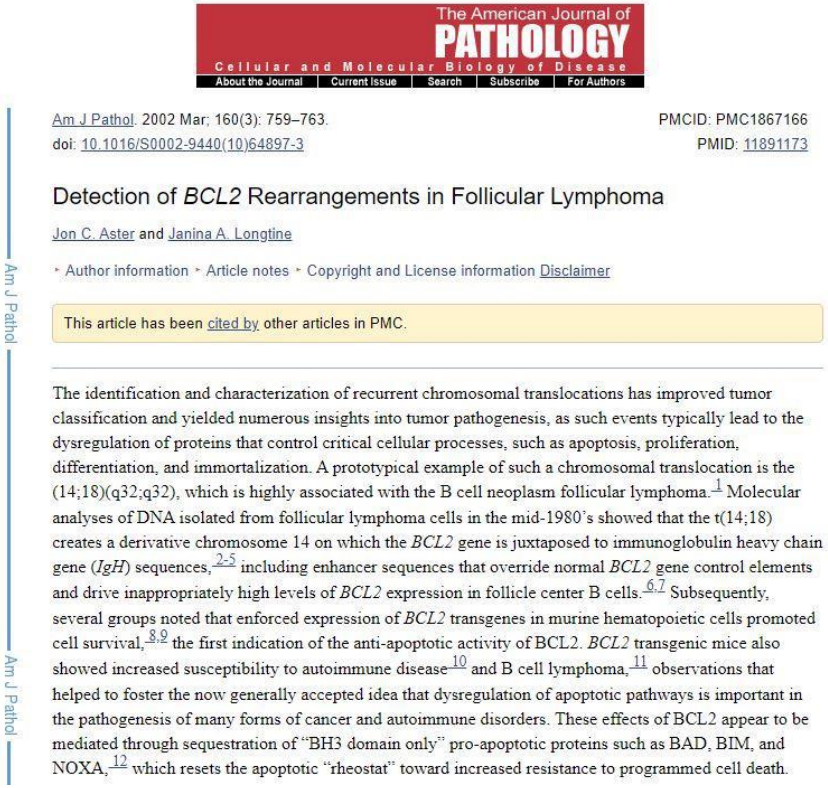
BCL2/JH Translocation

Related Publications:

- Aster et al. 2002: Detection of *BCL2* Rearrangements in Follicular Lymphoma

Why you should read it

- PCR as a reliable tool for *BCL-2* rearrangement detection



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Am J Pathol. 2002 Mar; 160(3): 759–763.
doi: 10.1016/S0002-9440(10)64897-3
PMCID: PMC1867166
PMID: 11891173

Detection of *BCL2* Rearrangements in Follicular Lymphoma

Jon C. Aster and Janina A. Longtine

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Am J Pathol

The identification and characterization of recurrent chromosomal translocations has improved tumor classification and yielded numerous insights into tumor pathogenesis, as such events typically lead to the dysregulation of proteins that control critical cellular processes, such as apoptosis, proliferation, differentiation, and immortalization. A prototypical example of such a chromosomal translocation is the (14;18)(q32;q32), which is highly associated with the B cell neoplasm follicular lymphoma.[1] Molecular analyses of DNA isolated from follicular lymphoma cells in the mid-1980's showed that the t(14;18) creates a derivative chromosome 14 on which the *BCL2* gene is juxtaposed to immunoglobulin heavy chain gene (*IgH*) sequences,[2-5] including enhancer sequences that override normal *BCL2* gene control elements and drive inappropriately high levels of *BCL2* expression in follicle center B cells.[6,7] Subsequently, several groups noted that enforced expression of *BCL2* transgenes in murine hematopoietic cells promoted cell survival,[8,9] the first indication of the anti-apoptotic activity of BCL2. *BCL2* transgenic mice also showed increased susceptibility to autoimmune disease[10] and B cell lymphoma,[11] observations that helped to foster the now generally accepted idea that dysregulation of apoptotic pathways is important in the pathogenesis of many forms of cancer and autoimmune disorders. These effects of BCL2 appear to be mediated through sequestration of "BH3 domain only" pro-apoptotic proteins such as BAD, BIM, and NOXA,[12] which resets the apoptotic "rheostat" toward increased resistance to programmed cell death.

Am J Pathol

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BCL2/JH t(14;18) Translocation

BCL2/JH t(14;18) Translocation

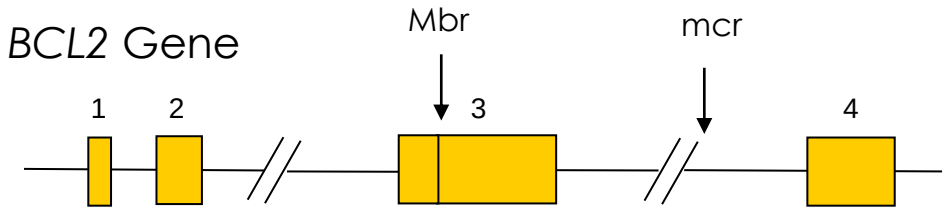
The **t(14;18)** joins the *BCL2* gene on **chromosome 18** to the *IGH* gene on **chromosome 14** leading **to inhibition of programmed cell** death through *BCL2* overexpression.

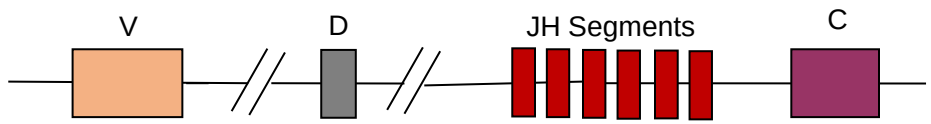
Target Background:

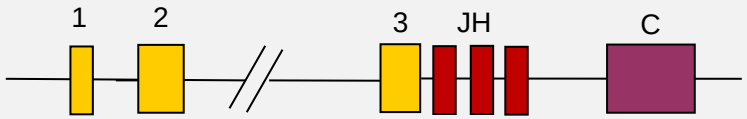
- *BCL2* t(14;18) translocations are detectable occurs in 70–90% of cases of **follicular lymphoma,** 20–30% of **diffuse large B-cell lymphoma**, and 5–10% of other less common subtypes.
- These translocations are not seen in other lymphomas; therefore, this test is useful for the differential diagnosis of B cell malignancies.
- Presence of the *BCL2* translocation is an indicator of poor prognosis in large cell diffuse B-cell lymphomas.
- Distinguish lymphoma from benign lymphoid hyperplasia
- Detect, monitor and evaluate disease recurrence

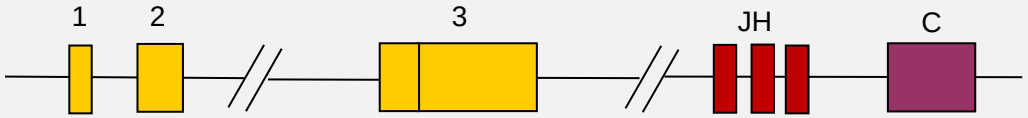
Chiu, C.-H. et al. The Utility of t(14;18) in Understanding Risk Factors for Non-Hodgkin Lymphoma Brian. J Natl Cancer Inst Monogr 2008;39:69–73

BCL2/JH t(14;18) Translocation



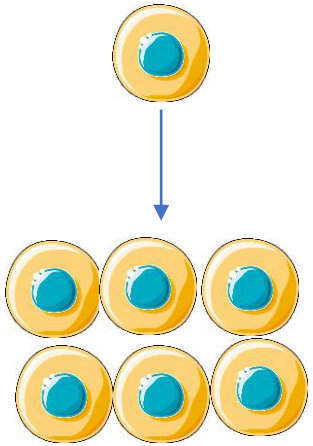






BCL2 gene under aberrant transcriptional control of IGH gene

Increased expression of BCL-2 protein



BCL-2 protein is an antagonist to apoptosis

Increased level of B-cells in the body

Mbr = Major Breakpoint Region
mcr = Minor Cluster Region

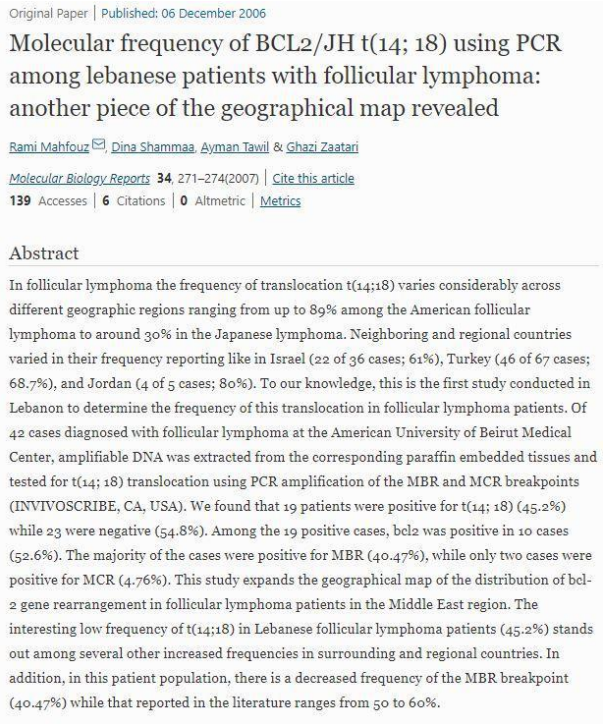
BCL2/JH t(14;18) Translocation

Related Publications:

- Mahfouz R. et al. 2007: Molecular Frequency of *BCL2/JH* t(14; 18) Using PCR Among Lebanese Patients With Follicular Lymphoma: Another Piece of the Geographical Map Revealed

Why you should read it

- PCR as a reliable tool for *BLC2/JH* t(14;18) detection in a geographical distribution study
- Low frequency of t(14;18) in Lebanese follicular Lymphoma patients with 45,2% vs. 80% in Jordan



Original Paper | Published: 06 December 2006

Molecular frequency of BCL2/JH t(14; 18) using PCR among lebanese patients with follicular lymphoma: another piece of the geographical map revealed

Rami Mahfouz, Dina Shammaa, Ayman Tawil & Ghazi Zaatari

Molecular Biology Reports **34**, 271–274(2007) | Cite this article

139 Accesses | **6** Citations | **0** Altmetric | Metrics

Abstract

In follicular lymphoma the frequency of translocation t(14;18) varies considerably across different geographic regions ranging from up to 89% among the American follicular lymphoma to around 30% in the Japanese lymphoma. Neighboring and regional countries varied in their frequency reporting like in Israel (22 of 36 cases; 61%), Turkey (46 of 67 cases; 68.7%), and Jordan (4 of 5 cases; 80%). To our knowledge, this is the first study conducted in Lebanon to determine the frequency of this translocation in follicular lymphoma patients. Of 42 cases diagnosed with follicular lymphoma at the American University of Beirut Medical Center, amplifiable DNA was extracted from the corresponding paraffin embedded tissues and tested for t(14; 18) translocation using PCR amplification of the MBR and MCR breakpoints (INVIVOSCRIBE, CA, USA). We found that 19 patients were positive for t(14; 18) (45.2%) while 23 were negative (54.8%). Among the 19 positive cases, bcl2 was positive in 10 cases (52.6%). The majority of the cases were positive for MBR (40.47%), while only two cases were positive for MCR (4.76%). This study expands the geographical map of the distribution of bcl-2 gene rearrangement in follicular lymphoma patients in the Middle East region. The interesting low frequency of t(14;18) in Lebanese follicular lymphoma patients (45.2%) stands out among several other increased frequencies in surrounding and regional countries. In addition, in this patient population, there is a decreased frequency of the MBR breakpoint (40.47%) while that reported in the literature ranges from 50 to 60%.

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BCR/ABL t(9;22) Translocation

BCR/ABL t(9;22) Translocation

The **Philadelphia chromosome** (Ph) is the result of reciprocal translocation, t(9;22)(q34;q11), of genetic material between the ***ABL1*** gene of **chromosome 9** and the ***BCR*** gene of **chromosome 22**.[1,2]

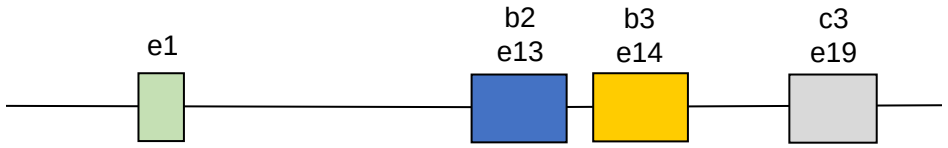
Target Background:

- The presence of this translocation is required for diagnosis of Chronic Myeloid Leukemia (**CML**)[3]
- Most common cytogenetic abnormality in adult Acute Lymphoblastic Leukemia (**ALL**; 20-30% of adult cases) and it occurs in 3-5% of pediatric cases[4]
- Detection, monitoring and evaluation of disease recurrence[4]

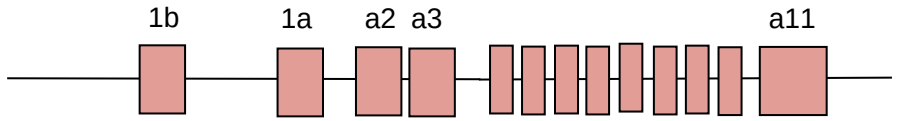
[1] Deininger, MWN, Goldman, JM and JV Melo. *Blood*, 2000, **96**:3343-3356
[2] Wapner J. *The Philadelphia Chromosome: A Genetic Mystery, a Lethal Cancer, and the Improbable Invention of a Lifesaving Treatment*. ISBN 9781615191970
[3] September 4th 2020: https://www.cancertherapyadvisor.com/home/decision-support-in-medicine/labmed/chronic-myeloid-leukemia-cml/
[4] Hong Hoe Koo, Philadelphia chromosome-positive acute lymphoblastic leukemia in childhood Korean J Pediatr. 2011 Mar; 54(3): 106–110

BCR/ABL t(9;22) Translocation

BCR Gene

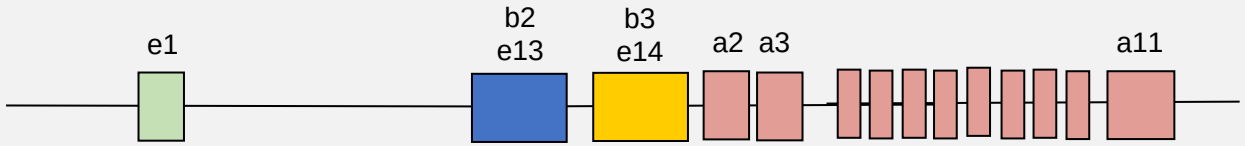


ABL Gene



Example of fusion gene, b2a2 junction

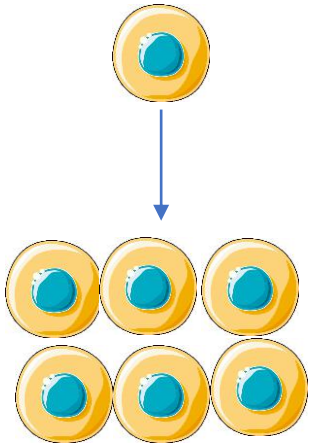
BCR/ABL Fusion Gene



ABL cDNA Control

Tests e1a2, e1a3, b2a2, b2a3, b3a2 and b3a3

p190, p210, p230 corresponds to the size (in kDa) of the proteins these transcripts encodes



Encodes proteins with aberrant tyrosine kinase activity

Responsible for leukemic phenotype

BCR/ABL t(9;22) Translocation

Related Publications:

- Kurzrock et al. 2003: Philadelphia Chromosome-Positive Leukemias: From Basic Mechanisms to Molecular Therapeutics

Why you should read it

- *BCR-ABL* inhibition is a remarkably successful targeted therapy approach for CML

Philadelphia Chromosome–Positive Leukemias: From Basic Mechanisms to Molecular Therapeutics

Razelle Kurzrock [1], Hagop M Kantarjian, Brian J Druker, Moshe Talpaz
Affiliations + expand
PMID: 12755554 DOI: 10.7326/0003-4819-138-10-200305200-00010

Abstract

The Philadelphia chromosome translocation (t(9;22)) results in the molecular juxtaposition of two genes, BCR and ABL, to form an aberrant BCR-ABL gene on chromosome 22. BCR-ABL is critical to the pathogenesis of chronic myelogenous leukemia and a subset of acute leukemias. The chimeric Bcr-Abl protein has constitutively elevated tyrosine phosphokinase activity. This abnormal enzymatic activation is critical to the oncogenic potential of Bcr-Abl. Initially, protein kinases were thought to be poor therapeutic targets because of their ubiquitous nature and crucial role in many normal physiologic processes. However, the advent of imatinib mesylate (Gleevec, Novartis Pharmaceuticals, Basel, Switzerland), formerly known as STI571 and CGP57148B, demonstrated that designer kinase inhibitors could be specific. This agent has shown striking activity in chronic myelogenous leukemia. It also inhibits phosphorylation of Kit (stem-cell factor receptor) and platelet-derived growth factor receptor. In addition, it has shown similar impressive responses, with little host toxicity, in gastrointestinal stromal tumors, which harbor activating Kit mutations, and in tumors with activated platelet-derived growth factor receptor. The studies of imatinib mesylate provide proof-of-principle for using aberrant kinases as a therapeutic target and are a model for the promise of molecular therapeutics. This paper reviews the current knowledge on the function of Bcr-Abl and its normal counterparts (Bcr and Abl), as well as the impact of this knowledge on the development of a remarkably successful targeted therapy approach.

BCR/ABL t(9;22) Translocation

Related Publications:

- Melo et al: The Diversity of *BCR-ABL* Fusion Proteins and their Relationship to Leukemia Phenotype

Why you should read it

- *BCR-ABL* translocation variants as indicators for Leukemia Phenotypes

Table 1. Types of Ph⁺ Leukemias Associated With Specific BCR Breakpoint Cluster Region (*bcr*) Rearrangements and Corresponding BCR-ABL Fusion Transcripts

Disease (references)	M-*bcr* BCR-ABL Fusion	m-*bcr* BCR-ABL Fusion	μ-*bcr* BCR-ABL Fusion
CML			
(8, 23, 25, 26, 36, 74)	b3a2 b2a2 b3a3 b2a3	e1a2	e19a2
ALL			
(9, 11, 27, 28, 70, 72, 73)	b3a2 b2a2 b3a3 b2a3	e1a2 e1a3 	
AML (12, 16, 27)	b3a2 b2a2	e1a2	
ET (60-62)	b3a2 b2a2		
MM (20)		e1a2	
B lymphoma (17)		e1a2	

Abbreviation: MM, multiple myeloma.

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PML/RARα t(15;17) Translocation

PML/RARa t(15;17) Translocation

This translocation involves the retinoic acid receptor alpha (**RARA**) gene on **chromosome 17** and the promyelocytic leukemia (**PML**) gene on **chromosome 15** that results in a **PML-RARA** fusion gene

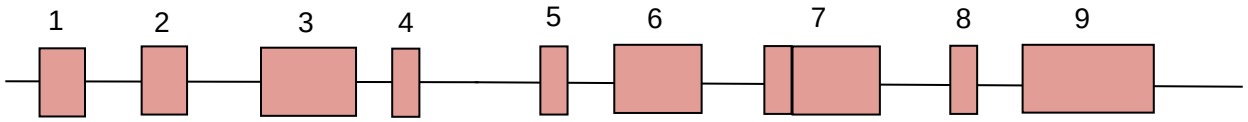
Target Background:

- Identification of **Acute Promyelocytic Leukemia** (APL) a form of **Acute Myeloid Leukemia** (AML)
- The *PML-RARA* fusion gene is the most critical event involved in the pathogenesis of APL
- Important for the **responsiveness** to all-trans-retinoic acid **(ATRA) treatment**
- Detection, monitoring and evaluation of disease recurrence

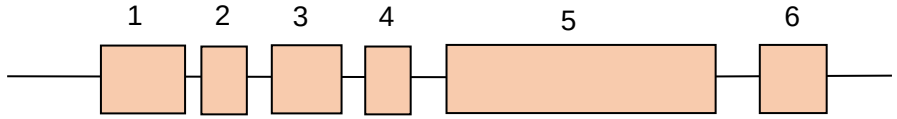
Liquori, A. et. al Acute Promyelocytic Leukemia: A Constellation of Molecular Events around a Single PML-RARA Fusion Gene. Cancers (Basel). 2020 Mar; 12(3): 624

PML/RARα t(15;17) Translocation

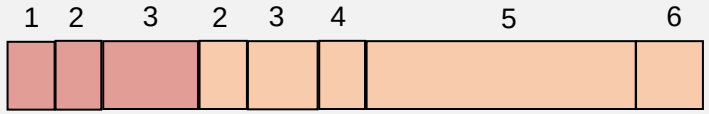
PML Gene



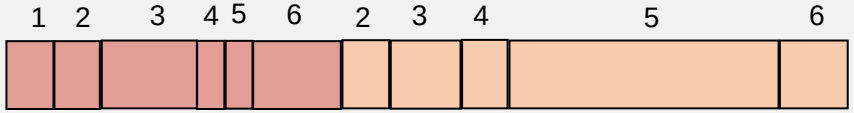
RARa Gene



PML/RARa Fusion Gene



(S-form rearrangement)



(L-form rearrangement)

PML/RARa rearrangements are correlated with **responsiveness to ATRA treatment**

PML/RARα t(15;17) Translocation

Related Publications:

- Gallagher et al 1995: Characterization of Acute Promyelocytic Leukemia Cases With *PML-RaRa* Break/Fusion Sites in PML Exon 6: Identification of a Subgroup With Decreased In Vitro Responsiveness to All-Trans Retinoic Acid

Why you should read it

- *PML-RARa* translocations as indication for responsiveness to Retinoic Acid treatment

Characterization of Acute Promyelocytic Leukemia Cases With PML-RARα Break/Fusion Sites in PML Exon 6: Identification of a Subgroup With Decreased In Vitro Responsiveness to All-*Trans* Retinoic Acid

By Robert E. Gallagher, Yun-Ping Li, Sreenivas Rao, Elisabeth Paietta, Janet Andersen, Polly Etkind, John M. Bennett, Martin S. Tallman, and Peter H. Wiernik

Of 113 acute promyelocytic leukemia cases documented to have diagnostic PML-RARα hybrid mRNA, 10 cases (8.8%) had fusion sites in PML gene exon 6 (V-forms) rather than in the two common hybrid mRNA configurations resulting from breaksites in either PML gene intron 6 (L-forms) or intron 3 (S-forms). In 4 V-form cases, a common break/fusion site was discovered at PML gene nucleotide (nt) 1685, abutting a 3′ cryptic splice donor sequence. The fusion site was proximal to the common site in 1 case and more distal in 5 cases. The open reading frame encoding a PML-RARα gene was consistently preserved, either by an in-frame fusion site or by the insertion of 3 to 127 unidentified nts. In 2 V-form cases, hybridization analysis of the reverse transcriptase-polymerase chain reaction products with a PML-RARα junction probe was required for discrimination from L-form cases. Two V-form subgroups were defined by in vitro sensitivity to all-*trans* retinoic acid (tRA)-induced differentiation: 4 of 4 cases tested with fusion sites at or 5′ to nt 1685 (subgroup E6S) had reduced sensitivity ($EC_{50} \geq 10^{-7}$ mol/L), whereas 4 of 4 cases with fusion sites at or 3′ to nt 1709 (subgroup E6L) had high sensitivity ($EC_{50} < 10^{-8}$ mol/L) indistinguishable from that of L-form and S-form cases. These results provide the first link between PML-RARα configuration and tRA sensitivity in vitro and support the importance of subclassifying APL cases according to PML-RARα transcript type.

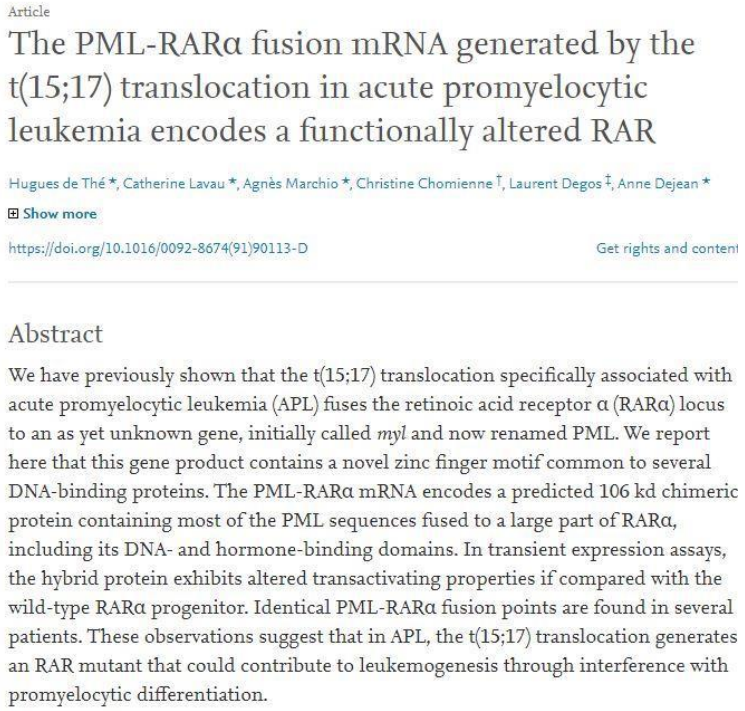
PML/RARα t(15;17) Translocation

Related Publications:

- De Thé et al. 1991: The *PML-RARα* fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR

Why you should read it

- *PML-RARα* Translocation contributes to Leukemogenesis through interference with promyelocytic differentiation



Article

The PML-RARα fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR

Hugues de Thé *, Catherine Lavau *, Agnès Marchio *, Christine Chomienne †, Laurent Degos ‡, Anne Dejean *

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Abstract

We have previously shown that the t(15;17) translocation specifically associated with acute promyelocytic leukemia (APL) fuses the retinoic acid receptor α (RARα) locus to an as yet unknown gene, initially called *myl* and now renamed PML. We report here that this gene product contains a novel zinc finger motif common to several DNA-binding proteins. The PML-RARα mRNA encodes a predicted 106 kd chimeric protein containing most of the PML sequences fused to a large part of RARα, including its DNA- and hormone-binding domains. In transient expression assays, the hybrid protein exhibits altered transactivating properties if compared with the wild-type RARα progenitor. Identical PML-RARα fusion points are found in several patients. These observations suggest that in APL, the t(15;17) translocation generates an RAR mutant that could contribute to leukemogenesis through interference with promyelocytic differentiation.

Thank You!

Any questions?

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