

Gene Section

Review

BCR (Breakpoint cluster region)

Ali G Turhan

Pole de Biologie-Sante - 40 avenue du Recteur Pineau - 86022 Poitiers Cedex, France (AGT)

Published in Atlas Database: August 2008

Online updated version : <http://AtlasGeneticsOncology.org/Genes/BCR.html>

DOI: 10.4267/2042/44509

This article is an update of :

Turhan AG. BCR (Breakpoint cluster region). *Atlas Genet Cytogenet Oncol Haematol* 2001;5(3):167-169.

Huret JL. BCR (Breakpoint cluster region). *Atlas Genet Cytogenet Oncol Haematol* 1997;1(2):43-45.

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2009 *Atlas of Genetics and Cytogenetics in Oncology and Haematology*

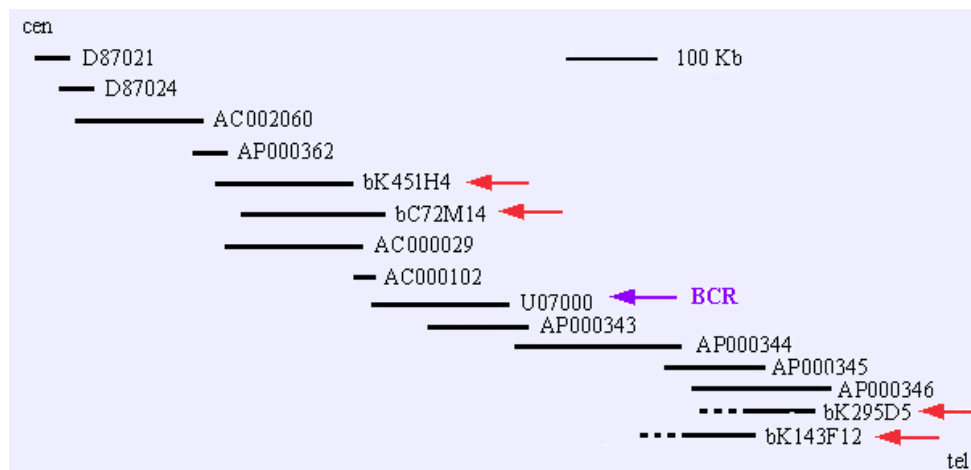
Identity

Other names: BCR1; PHL (Philadelphie)

HGNC (Hugo): BCR

Location: 22q11.2

Local order: Distal to IGL in 22q11.1, proximal to EWS and NF2, both in 22q12.



Map of the BCR region; - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

DNA/RNA

Description

About 23 exons; 130 kb; 5' centromere - 3' telomere orientation.

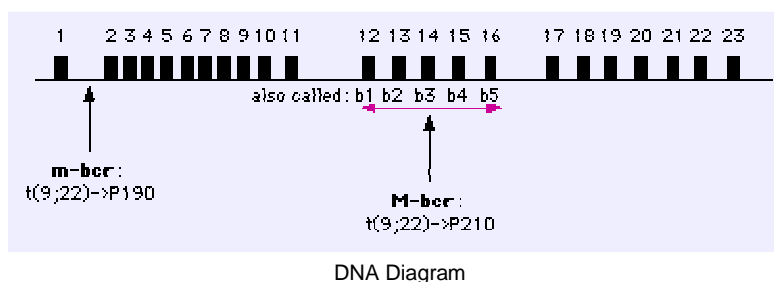
Transcription

Into various mRNA, of which are 4.5 kb and 7 kb.

Protein

Description

130 kDa, 190 kDa; mainly 160 kDa (1271 amino acids); N-term ATP binding/Serine-Threonine kinase domain, SH2 binding, GTP/GDP exchange domain, and C-term domain which functions as a GTPase activating protein for p21rac.



Expression

Ubiquitously expressed, with highest expression in brain and hematopoietic tissue.

Localisation

Cytoplasmic.

Function

Protein (serine/threonine) kinase; includes major signalisation domains such as:

- oligomerization domain, responsible of homotetramerization of BCR-ABL molecule and necessary for its transforming potential;
- serine threonine kinase domain, including at least three SH2 binding sites; able to interact with proteins with SH2 domains: These sites include TYR177, necessary for binding of Grb2 and activation of RAS pathway and beta-isoform of 14-3-3 proteins;
- GEF domain, in which lies the binding activity to the xeroderma pigmentosum protein, involved in DNA repair;
- a COOH-terminal RAC-GAP domain which does not participate to hybrid BCR-ABL proteins.

From the functional point of view, the role of bcr has been studied in bcr-null mice which show an increased respiratory burst suggesting the involvement of bcr protein in the regulation of superoxide production, probably via RAC.

In the context of CML, the role of bcr protein has been studied in in vitro and in vivo models; bcr gene has been shown to be a negative regulator of BCR-ABL. Its reduced expression increases the transforming potential of BCR-ABL. When overexpressed, bcr blocks BCR-ABL-mediated transformation in experimental mouse models. Serine 354 is required for the inhibitory function of bcr over BCR-ABL, as kinase mutants of bcr overexpressed in BCR-ABL expressing cells induce an increased tumorigenicity.

Homology

Drosophila rotund protein; other guanine-nucleotide releasing factors of the CDC24 family.

Implicated in

t(9;22)(q34;q11)/chronic myelogenous leukemia (CML) --> BCR / ABL

Disease

All CML have a t(9;22), at least at the molecular level (BCR/ABL); phenotype and stem cell origin: multipotent progenitor: t(9;22) is found in all myeloid and B- lineage progenitors.

Prognosis

The prognosis of CML has changed radically over the last 10 years, due to the development of novel drugs able to target the enhanced tyrosine kinase activity of BCR-ABL. The first of these therapies is Imatinib Mesylate (Gleevec) which has become the first line therapy for all patients with CML (See ABL and CML). In the first cohort trial of patients treated with Imatinib mesylate, the rates of complete cytogenetics responses (CCR) were exceptionally high (82%) as compared to standard IFN-alpha - ARA-C therapy. At the most recent 6-year update, the overall survival is 90% and most interestingly, the rates of progression towards more aggressive phases have been found to be progressively decreasing in all patients with major molecular responses (MMR). (For definition of MMR see CML). In IM-resistant or relapsing Ph1+ CML patients, second generation tyrosine kinase inhibitor (TKI) therapies such as Dasatinib (a dual SRC and ABL inhibitor) and Nilotinib have also recently become available.

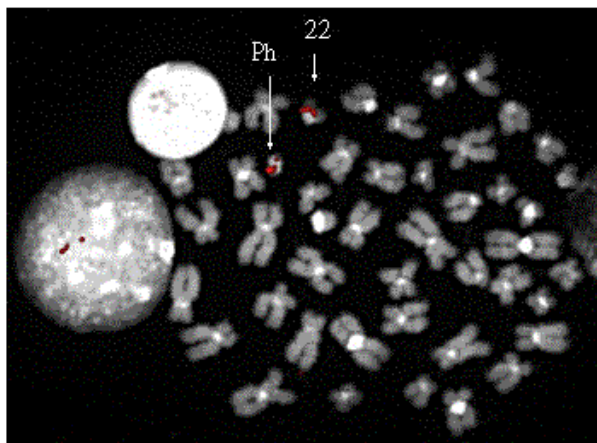
Cytogenetics

Anomalies additional to the t(9;22) may be found either at diagnosis or during course of the disease, or at the time of acute transformation; mainly: +der(22), +8, i(17q), +19; +21, -Y, -7, -17,+17; variant translocations: t(9;22;V) and apparent t(V;22) or t(9;V), where V is a variable chromosome, karyotypes with apparently normal chromosomes 9 and 22, may be found.

Deletion of the derivative chromosome 9: Detected at diagnosis (in 10% of patients), probably indicating a genetic instability phenotype, this finding has been associated to the more aggressive behavior of the disease, a poor prognostic factor potentially reversed by the use of imatinib mesylate.

Hybrid/Mutated gene

See below.



72M14 on a case of CML with t(9/22). Note that the probe remains on der(22) (Ph) - Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics .

Abnormal protein

See below.

Oncogenesis

See below.

t(9;22)(q34;q11)/acute lymphoblastic leukemia (ALL) --> BCR / ABL

Disease

Most often CD 10+ B-ALL; frequent CNS involvement.

Prognosis

The prognosis of Ph1+ ALL has changed since the introduction of tyrosine-kinase inhibitor therapies, especially imatinib mesylate which is currently used as a first line therapy associated with either high dose chemotherapy or classical ALL-type induction (steroids+ vincristine) and maintenance. Allogeneic stem cell transplantation is indicated in Ph1+ ALL patients relapsing after Imatinib-based regimens. In IM-resistant or relapsing Ph1+ ALL patients, second generation tyrosine kinase inhibitor (TKI) therapies such as Dasatinib (a dual SRC and ABL inhibitor) and Nilotinib have also recently become available.

Cytogenetics

The chromosome anomaly t(9;22) disappear during remission, in contrast with BC-CML cases (CML in blast crisis); additional anomalies: +der(22), -7, del(7q) most often, +8, but not an i(17q), in contrast with CML and AML cases; complex karyotypes, often hyperploid; variants and complex translocations may be found as in CML.

Hybrid/Mutated gene

See below. In Both CML and Ph1+ ALL, detection and quantification of p210 BCR-ABL and p190 BCR-ABL have become the cornerstones of monitoring targeted therapies.

Abnormal protein

See below.

Oncogenesis

See below.

t(9;22)(q34;q11)/acute myeloid leukemia (AML) --> BCR / ABL

Disease

AML mostly M1 or M2 AML

Prognosis

High rates of hematologic, cytogenetic and molecular responses have been reported in de novo PH1+ AML, which is a rare entity.

Cytogenetics

The chromosome anomaly t(9;22) disappear during remission, in contrast with BC-CML cases (CML in blast crisis); additional anomalies: similar to what is found in CML.

Hybrid/Mutated gene

BCR/ABL the crucial event lies on der(22), id est 5' BCR - 3' ABL hybrid gene is the crucial one, while ABL/BCR may or may not be expressed; Breakpoint in ABL is variable over a region of 200 kb, often between the two alternative exons 1b and 1a, sometimes 5' of 1b or 3' of 1a, but always 5' of exon 2; breakpoint in BCR is either:

- 1- in a region called M-bcr (for major breakpoint cluster region), a cluster of 5.8 kb, between exons 12 and 16, also called b1 to b5 of M-bcr; most breakpoints being either between b2 and b3, or between b3 and b4; transcript is 8.5 kb long; this results in a 210 kDa chimeric protein (P210); this is found in (most cases of) CML, and in half cases of ALL or AML.
- 2- in a 35 kb region between exons 1 and 2, called m-bcr (minor breakpoint cluster region), -> 7 kb mRNA, resulting in a 190 kDa protein (P190) found in approximately 25% of adult ALL cases.
- 3- A breakpoint in the exon 19 of BCR (designed as the micro-bcr) with fusion to abl sequences (a2) has been found in neutrophilic CML, with presence of a larger protein (P230).

Abnormal protein

BCR/ABL P210 comprises the first 902 or 927 amino acids from N-term of BCR, whereas P190 BCR and P230 include 427 and 1176 aminoacids respectively, from the N-term region of BCR; BCR/ABL has a cytoplasmic localization, probably by the ability of the oligomerization domain to interact with F-actin. ABL is both nuclear and cytoplasmic, due to the presence of nuclear localisation and export signals (NLS and NES) within its COOH terminal region.

Oncogenesis

All three forms of BCR-ABL oncogenes have transforming potential and it is now clear that they are responsible for initiation of the leukemic process associated with BCR-ABL oncogenes: Several signalling pathways are simultaneously activated and some phenotypic correlations can be made with the molecular abnormalities:

1- constitutive activation of RAS pathway (via TYR177 of the BCR) mimicking the growth-factor-stimulation of cells, leads to a proliferative behavior;

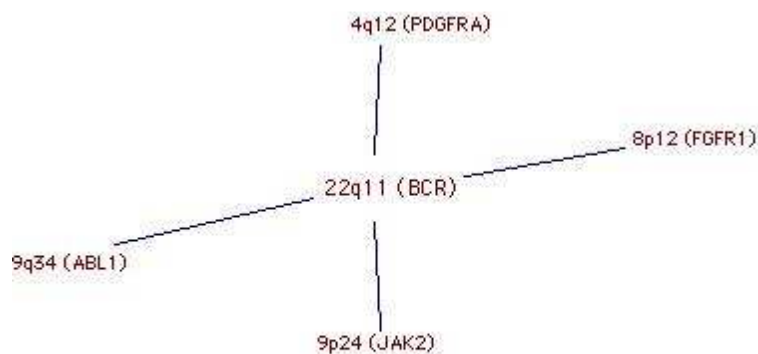
2- activation of PI-3K/Akt as well as JAK/STAT pathways is most likely responsible for the anti-apoptotic potential;

3- BCR/ABL provokes cell adhesive abnormalities (via CRK-L, FAK) as well as abnormalities of cell migration (via CXCR-4 whose expression is downregulated in CML cells expressing high levels of BCR-ABL). In experimental settings CD44 has been shown to play a major role in homing of BCR-ABL expressing cells. Activation of focal adhesion

molecules (FAK /) via CRK-L as well as abnormal response to SDF-1 leads to adhesive and migratory abnormalities of leukemic cells. It should be noted that specific signalling events leading to ALL with P190 and to CML with P210 have not been clearly established. A differential activation of Rho protein could play a role between the two phenotypes: rho Rac and cdc42 interact with BCR-ABL p210 but BCR-ABL p190 activates rac and cdc42 only. Deletion of Ikaros, has recently been implicated as a major oncogenic event cooperating with BCR-ABL in the BCR-ABL+ ALL.

Progression to blast crisis in CML: multiple events could be involved, with the major phenotype being a genetic instability: 1- mutation of P53, 2- methylation of internal ABL promoter; 3- telomere shortening; 4- inhibition of negative regulators of BCR-ABL (such as Abi-1) 5- BCR-ABL induces a major genetic instability: molecular pathways involved in this phenomenon have recently been elucidated (see ABL AND CML).

Breakpoints



BCR and partners. Editor 08/2004; last update 08/2005; last update 05/2008

References

Hariharan IK, Adams JM. cDNA sequence for human bcr, the gene that translocates to the abl oncogene in chronic myeloid leukaemia. *EMBO J.* 1987 Jan;6(1):115-9

Hermans A, Heisterkamp N, von Linden M, van Baal S, Meijer D, van der Plas D, Wiedemann LM, Groffen J, Bootsma D, Grosveld G. Unique fusion of bcr and c-abl genes in Philadelphia chromosome positive acute lymphoblastic leukemia. *Cell.* 1987 Oct 9;51(1):33-40

Voncken JW, van Schaick H, Kaartinen V, Deemer K, Coates T, Landing B, Pattengale P, Dorseuil O, Bokoch GM, Groffen J. Increased neutrophil respiratory burst in bcr-null mutants. *Cell.* 1995 Mar 10;80(5):719-28

Takeda N, Shibuya M, Maru Y. The BCR-ABL oncoprotein potentially interacts with the xeroderma pigmentosum group B protein. *Proc Natl Acad Sci U S A.* 1999 Jan 5;96(1):203-7

Wu Y, Ma G, Lu D, Lin F, Xu HJ, Liu J, Arlinghaus RB. Bcr: a negative regulator of the Bcr-Abl oncoprotein. *Oncogene.* 1999 Aug 5;18(31):4416-24

Deininger MW, Goldman JM, Melo JV. The molecular biology of chronic myeloid leukemia. *Blood.* 2000 Nov 15;96(10):3343-56

Deutsch E, Dugray A, AbdulKarim B, Marangoni E, Maggiorella L, Vaganay S, M'Kacher R, Rasy SD, Eschwege F, Vainchenker W, Turhan AG, Bourhis J. BCR-ABL down-regulates the DNA repair protein DNA-PKcs. *Blood.* 2001 Apr 1;97(7):2084-90

Laurent E, Talpaz M, Kantarjian H, Kurzrock R. The BCR gene and Philadelphia chromosome-positive leukemogenesis. *Cancer Res.* 2001 Mar 15;61(6):2343-55

Arlinghaus RB. Bcr: a negative regulator of the Bcr-Abl oncoprotein in leukemia. *Oncogene.* 2002 Dec 9;21(56):8560-7

Perrotti D, Cesi V, Trotta R, Guerzoni C, Santilli G, Campbell K, Iervolino A, Condorelli F, Gambacorti-Passerini C, Caligiuri MA, Calabretta B. BCR-ABL suppresses C/EBPalpha expression through inhibitory action of hnRNP E2. *Nat Genet.* 2002 Jan;30(1):48-58

Harnois T, Constantin B, Rioux A, Grenioux E, Kitzis A, Bourmeyster N. Differential interaction and activation of Rho family GTPases by p210bcr-abl and p190bcr-abl. *Oncogene*. 2003 Sep 25;22(41):6445-54

Calabretta B, Perrotti D. The biology of CML blast crisis. *Blood*. 2004 Jun 1;103(11):4010-22

Krause DS, Lazarides K, von Andrian UH, Van Etten RA. Requirement for CD44 in homing and engraftment of BCR-ABL-expressing leukemic stem cells. *Nat Med*. 2006 Oct;12(10):1175-80

Mullighan CG, Miller CB, Radtke I, Phillips LA, Dalton J, Ma J, White D, Hughes TP, Le Beau MM, Pui CH, Relling MV,

Shurtleff SA, Downing JR. BCR-ABL1 lymphoblastic leukaemia is characterized by the deletion of Ikaros. *Nature*. 2008 May 1;453(7191):110-4

Perazzona B, Lin H, Sun T, Wang Y, Arlinghaus R. Kinase domain mutants of Bcr enhance Bcr-Abl oncogenic effects. *Oncogene*. 2008 Apr 3;27(15):2208-14

This article should be referenced as such:

Turhan AG. BCR (Breakpoint cluster region). *Atlas Genet Cytogenet Oncol Haematol*. 2009; 13(7):469-473.
