Atlas of Genetics and Cytogenetics
in Oncology and Haematology

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Gene Section
Mini Review

BCR (breakpoint cluster region)

Jean-Loup Huret

Genetics, Department of Medical Information, University of Poitiers, CHU Poitiers Hospital, F-86021 Poitiers, France

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Identity

Other names: BCR1, PHL
Location: 22q11.2
Local order: Distal to IGL in 22q11.1, proximal to EWS, NF2, both in 22q12.

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.

Localisation

Cytoplasmic.

Function

Protein (serine/threonine) kinase; probable signal transduction activity.

Homology

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

Implicated in

t(9;22)(q34;q11)/CML ⟶ BCR/ABL

Disease

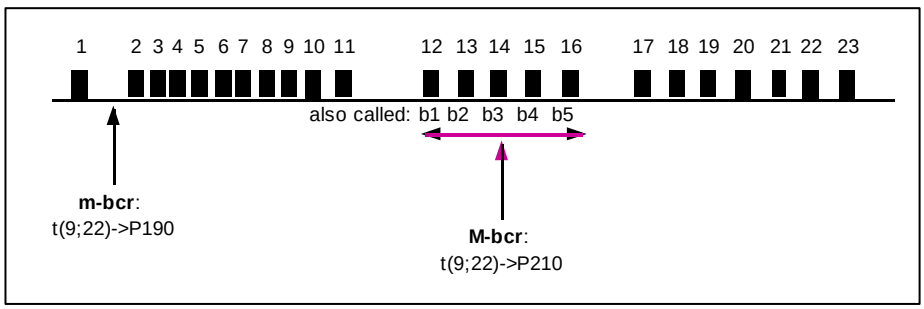
All CML have a t(9;22), at least at the molecular level (BCR/ABL); phenotype and stem cell origin: multipotent progenitor: t(9;22) is found in all myeloid and B-lineage progenitors.

Prognosis

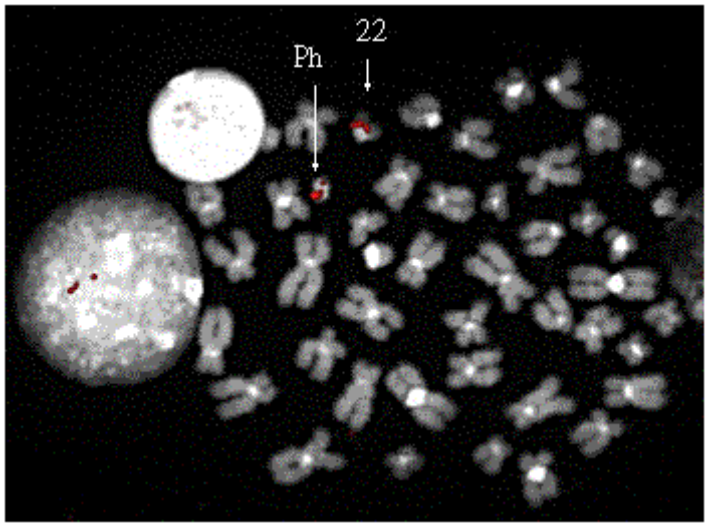
Median survival ≥ 4 yrs; alphaIFN therapy or BMT are indicated.

Cytogenetics

Anomalies additional to the t(9;22) may be found either at diagnosis or during course of the disease, or at the



DNA diagram



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

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.

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 ANLL;
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); this is found in half of the cases of ALL or ANLL.

Abnormal Protein

BCR/ABL P210 comprises the first 902 or 927 amino acids from BCR, P190 only the 427 N-term from BCR; BCR/ABL has a cytoplasmic localization, in contrast with ABL, mostly nuclear.

Oncogenesis

That BCR/ABL has a cytoplasmic localization may have a carcinogenetic role. The hybrid protein has an increased protein kinase activity compared to ABL: 3BP1 (binding protein) binds normal ABL on SH3 domain, which prevents SH1 activation; with BCR/ABL, the first (N-terminal) exon of BCR binds to SH2, hidding SH3 which, as a consequence, cannot be bound to 3BP1; thereof, SH1 is activated. Oncogenesis:
1-proliferation is induced through activation by BCR/ABL of RAS signal transduction pathway, PI3-K (phosphatidyl inositol 3' kinase) pathway, and MYC;
2-BCR/ABL inhibits apoptosis;
3-BCR/ABL provokes cell adhesive abnormalities.

t(9;22)(q34;q11)/ALL ⟶ BCR/ABL

Disease

Most often CD10+ ALL; frequent CNS involvement.

Prognosis

Is very poor (BMT is indicated); the breakpoint in M-bcr or in m-bcr (see below) does not seem to have impact on prognosis.

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 ANLL cases; Complex karyotypes, often hyperploid; variants and complex translocations may be found as in CML.

Hybrid/Mutated Gene

See above.

Abnormal Protein

See above.

Oncogenesis

See above.

t(9;22)(q34;q11)/ANLL ⟶ BCR/ABL

Disease

ANLL mostly M1 or M2 ANL.

Prognosis

Is very poor.

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

See above.

Abnormal Protein

See above.

Oncogenesis

See above.

References

Kurzrock R, Talpaz M. The molecular pathology of chronic myelogenous leukemia. Br J Haematol 1991 Oct;79 Suppl 1:34-7. (Review).

Heisterkamp N, Groffen J. Molecular insights into the Philadelphia translocation. Hematol Pathol 1991;5(1):1-10. (Review).

Gotoh A, Broxmeyer HE. The function of BCR/ABL and related proto-oncogenes. Curr Opin Hematol 1997 Jan;4(1):3-11.

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