Gene Section
Mini Review

ABL (v-abl Abelson murine leukemia viral oncogene homolog 1)
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Identity
Other names: ABL1
Location: 9q34.1
Local order: CAN is more telomeric, TAN1 even more in 9q34.3.

DNA/RNA
Description
12 exons; 230 kb.

Transcription
Alternate splicing: 1a and 1b are 5’ alternative exons; mRNA of 6 and 7 kb (with 1a and 1b respectively), giving rise to 2 proteins of 145 kDa.

Protein
Description
1130-1143 amino acids; 4 domains: of which are SH (SRC homology) domains; NH2-term -- domain 1: SH3 (where can bind the binding protein BP1, to inhibit SH1 activation) and SH2 (with high affinity towards BCR first exon) -- domain 2: SH1 (with a self-phosphorylable tyrosine) -- domain 3: nuclear localization domain (DNA binding, but not during mitosis) -- domain 4: actin binding (cytoskeleton) -- COOH-term; note: 1b (but not the 1a alternative) myristylable allowing anchorage to the membrane.

Expression
Ubiquitously expressed.

Localisation
Mainly nuclear (tyrosine kinases are usually cytoplasmic); can migrate into the cytoplasm.

Function
Inhibits cell growth through a direct interaction with Rb in the nucleus.

Homology
SRC homology; like SRC, ABL is one of the tyrosine kinases which are not membrane receptors.

DNA diagram
Implicated in

t(9;12)(q34;p12)/ALL $\rightarrow$ ETV6/ABL

Disease
Common ALL; yet poorly known.

Hybrid/Mutated Gene
5' ETV6/TEL from 12p12 - 3' ABL from 9q34.

Abnormal Protein
NH2-term Helix Loop Helix from ETV6(TEL) fused to Tyr kinase from ABL COOH-term; localised in the cytoskeleton.

Oncogenesis
Forms HLH-dependent oligomers, which may be critical for Tyr kinase activation; oncogenesis may be comparable to that induced by BCR/ABL.

Prognosis
Median survival $\geq$ 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 time of acute transformation; mainly: +der(22), +8, t(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 carcinogenic 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, hiding 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 (phosphatidylinositol 3' kinase) pathway, and MYC;
2-BCR/ABL inhibits apoptosis;
3-BCR/ABL provokes cell adhesive abnormalities.
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Huret JL

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**Probe 1132H12 on a case of CML with t(9/22). Note the splitting of the probe, evident also on interphase nuclei.**

Courtesy Mariano Rocchi, Resources for Molecular Cytogenetics.

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**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) disappears 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.

**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.

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**t(9;22)(q34;q11)/ANLL → BCR/ABL**

**Disease**

ANLL mostly M1 or M2 ANL.

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**References**


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This article should be referenced as such: