

Molecular genetics of chronic myeloid leukemia

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INTRODUCTION

Chronic myeloid leukemia (CML, also known as chronic myelocytic, myelogenous, or granulocytic leukemia) is classified as one of the myeloproliferative neoplasms, along with polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). (See "Overview of the myeloproliferative neoplasms".)

This group of diseases shares several distinct features:

- They are clonal disorders of hematopoiesis that arise in a hematopoietic stem or early progenitor cell.
- They are characterized by the dysregulated production of a particular lineage of mature myeloid cells with fairly normal differentiation.
- They exhibit a variable tendency to progress to acute leukemia.
- They share abnormalities of hemostasis and thrombosis.

The individual myeloproliferative neoplasms predominantly affect a single myeloid cell type, resulting in an excess of neutrophils in CML, erythrocytes in PV, and platelets in ET. However, there is considerable overlap between the clinical features as patients with CML, for example, often have thrombocytosis.

CML is almost invariably associated with an abnormal chromosome 22 known as the Philadelphia chromosome, often abbreviated as Ph, Ph(1), or Ph¹ [1,2]. The Philadelphia chromosome t(9;22)(q34;q11) results in the formation of a unique gene product (BCR-ABL1), which is a constitutively active tyrosine kinase. This deregulated tyrosine kinase is implicated in the development of CML and has become a primary target for the treatment of this disorder.

The molecular genetics of the Philadelphia chromosome will be reviewed here. How the BCR-ABL1 fusion protein product of the Philadelphia chromosome promotes leukemogenesis is discussed separately. (See "Cellular and molecular biology of chronic myeloid leukemia".)

THE PHILADELPHIA CHROMOSOME

The Philadelphia (Ph) chromosome was originally detected by workers in Philadelphia as an abnormally short G-group chromosome in analysis of bone marrow metaphases from CML patients [3]; it has the distinction of being the first genetic abnormality to be associated with a human cancer. Subsequently, advances in chromosome banding techniques demonstrated that the Ph chromosome was the result of a balanced translocation between chromosomes 9 and 22, denoted t(9;22) (q34.1;q11.21), where the derivative chromosome 22 is significantly smaller (figure 1) [4]. The Ph chromosome is present in hematopoietic cells from patients with CML but not in nonhematopoietic tissues, including bone marrow fibroblasts [5]; thus, the Ph chromosome is acquired and not inherited through the germline.

Nomenclature — A standardized nomenclature is used to describe genes, mRNA transcripts, and gene products (ie, proteins). Human genes are designated by *italicized* CAPITAL letters (eg, *BCR-ABL1* gene), while human proteins are designated by non-italicized CAPITAL letters (eg, BCR-ABL1 protein). Proteins may also be designated by the prefix "p" with the molecular weight in kilodaltons (kD), followed by the gene name in superscript (eg, p210 ^{BCR-ABL1} protein).

Structure of the Philadelphia chromosome — The structure of the Ph chromosome was established by recognition of the translocation of the *ABL1* gene on chromosome 9q34 to the Ph chromosome [6], and the subsequent identification of breakpoints near the 5' end of *ABL1* in leukemic cells from patients with CML [7]. *ABL1* had been previously identified as the cellular homologue of the transforming gene of Abelson murine leukemia virus (v-Abl) [8], an acutely transforming retrovirus that induces B-lymphoid leukemia in mice [9]. The *ABL1* gene on chromosome 9 has 11 exons with two alternative 5' first exons, and a very large first intron of over 250 kilobases (kb). *ABL1* encodes a non-receptor protein-tyrosine kinase, ABL1 (figure 2). (See "Cellular and molecular biology of chronic myeloid leukemia", section on 'ABL1'.)

DNA sequences immediately 5' to *ABL1* on the Ph chromosome were derived from chromosome 22 sequences, and DNA probes from a small region on chromosome 22 detected genomic rearrangements by Southern blot analysis of genomic DNA in virtually all CML samples [10]. This locus on chromosome 22 was named the **breakpoint cluster region**, or bcr, in the middle of a large protein-coding gene of 25 exons, now called the *BCR* gene. Five small exons were initially identified in the bcr region and denoted exons b1 through b5; they are now known to be exons 12 through 16 of the major breakpoint cluster region (M-BCR). *BCR* encodes a 160 kD cytoplasmic phosphoprotein denoted BCR. (See "Cellular and molecular biology of chronic myeloid leukemia", section on 'BCR'.)

Depending on the location of the breakpoint within *BCR*, the consequence of the t(9;22) translocation in CML is to fuse the first 13 or 14 exons of *BCR* upstream of the second exon of *ABL1*, with the breakpoint on chromosome 9 falling in the large first intron region. The two alternative fusion genes are traditionally described according to the original bcr exon nomenclature as b2a2 and b3a2 fusions or by the subsequent nomenclature as e13a2 or e14a2, respectively. Transcription of the fusion gene followed by RNA splicing leads to the generation of a novel 8.5 kb fusion *BCR-ABL1* mRNA that encodes a fusion protein of 210 kD designated p210 BCR-ABL1 or p210^{BCR-ABL1} [11]. The protein product of the b3a2 fusion is 25 amino acids longer than the b2a2 product due to the inclusion of the b3 exon. (See "Cellular and molecular biology of chronic myeloid leukemia", section on 'BCR-ABL1').

Distinct forms of BCR-ABL1 from alternative chromosome 22 breakpoints — Several years after the description of BCR-ABL1 in patients with CML, it was discovered that the majority of pediatric and adult patients with Ph-positive B-ALL had chromosome 22 breakpoints within the large first intron of *BCR* rather than the classic bcr region, leading to formation of a smaller *BCR-ABL1* fusion gene consisting of the first exon of *BCR* fused upstream of *ABL1* exon 2 (e1a2) [12,13]. The bcr region in CML was renamed the major or M-bcr, while the first intron breakpoints were designated the minor or m-bcr. This fusion generates a protein of 190 kD in size, p190^{BCR-ABL1} that contains *BCR* first exon-encoded sequence fused to the same amount of *ABL1* found in p210 [14]. A third minor *BCR* region (mu-BCR) on chromosome 22 resulting in fusion of *BCR* exon 19 to *ABL1* exon 2 (e19a2) has been described in several patients, leading to generation of a p230 form of BCR-ABL1 (figure 2) [15].

As such, there are three common variants of BCR-ABL1 (figure 2):

- p210^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in the major *BCR* region at either e13 or e14 to produce an e13a2 or e14a2 transcript which is translated into a 210 kD protein. This variant is present in most patients with CML and one-third of those with Ph-positive B cell acute lymphoblastic leukemia (Ph+ B-ALL).

- p190^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in the minor *BCR* region at e1 to produce an e1a2 transcript which is translated into a 190 kD protein. This variant is present in two-thirds of those with Ph+ B-ALL and a minority of patients with CML.
- p230^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in the mu *BCR* region at e19 to produce an e19a2 transcript which is translated into a 230 kD protein. This variant is seen in some patients with chronic neutrophilic leukemia. (See 'p190 and p230 fusion proteins' below.)

In addition to these more common variant forms, rare patients with fusion of *BCR* exon 1 or exon b2 to *ABL1* exon 3 (e1a3 and b2a3) and *BCR* exon 6 to *ABL1* exon 2 (e6a2) have been described, where both fusion mRNAs are predicted to have an intact translational reading frame [16].

Reciprocal translocation product — The reciprocal translocation product on the derivative chromosome 9, notated as der(9), is an *ABL1-BCR* fusion gene that could generate an ABL1-BCR fusion protein. However, the inconsistent expression of the *ABL1-BCR* gene in patients with CML, along with survival data in *ABL1-BCR* negative patients, suggest that this product does not play a major role in the pathogenesis of this disorder [17,18]. Some studies have suggested that der(9) deletions may confer a worse prognosis in patients with CML marked by lower response rates and a shorter progression-free survival [19-22]. However, deletion of der(9) may no longer be a marker of poor prognosis among patients treated with tyrosine kinase inhibitors. As an example, combined data from 521 patients enrolled in three prospective trials with a median follow-up of 42 months demonstrated that der(9) deletions detected by FISH did not confer a worse prognosis for patients with early chronic phase CML treated with imatinib [22].

Leukemogenesis — The development of chronic phase CML appears to be a direct result of BCR-ABL1 activity, which promotes its development by allowing:

- Uncontrolled proliferation of transformed cells
- Discordant maturation
- Escape from apoptosis
- Altered interaction with the cellular matrix

The progression of CML from chronic phase to accelerated phase or blast crisis is a complex, multistep process, but also appears to involve the constitutive expression of the BCR-ABL1 tyrosine kinase. The role of BCR-ABL1 in the pathogenesis of CML is presented in more detail separately. (See "Cellular and molecular biology of chronic myeloid leukemia".)

Detecting the Philadelphia chromosome or its products — The World Health Organization (WHO) diagnostic criteria for CML require the detection of the Ph chromosome or its products, the *BCR-ABL1* fusion mRNA and the BCR-ABL1 protein. This can be accomplished through conventional cytogenetic analysis (karyotyping), FISH analysis, or by RT-PCR. Southern blot techniques to identify *BCR-ABL1* gene rearrangements were used in the past but are time consuming and no longer employed as a routine diagnostic test. Evaluating for BCR-ABL1 protein by Western blot analysis is also not commonly used. (See "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Genetics'.)

Cytogenetics — The Ph chromosome was initially discovered by cytogenetic analysis using May-Grünwald-Giemsa (MGG) banded metaphase chromosomes from marrow or peripheral blood. However, this technique requires in vitro culture, is time- and labor-intensive, has a sensitivity limit of detection of about 5 percent Ph-positive cells in a population of normal cells, and can give false negative results in cells with complex chromosomal rearrangements.

FISH — Fluorescence in situ hybridization (FISH) employs large DNA probes linked to fluorophores; it permits direct detection of the chromosomal position of the *BCR* and *ABL1* genes when employed with metaphase chromosome preparations. It can also be utilized on interphase cells from bone marrow or peripheral blood, in which physical co-localization of *BCR* and *ABL1* probes is indicative of the presence of the *BCR-ABL1* fusion gene (figure 3) [23]. The specificity of metaphase FISH is higher than MGG banding for detection of the Ph chromosome and allows easy identification of complex chromosomal rearrangements that mask the t(9;22) translocation. Although most FISH techniques cannot distinguish among different chromosome 22 breakpoints, some commercially available probes allow detection of a range of chromosome 9 breakpoints [24,25].

RT-PCR — Reverse-transcription polymerase chain reaction (RT-PCR) is a highly sensitive technique that employs specific primers to amplify a DNA fragment from *BCR-ABL1* mRNA transcripts. Depending on the combination of primers used, the method can detect the e1a2, e13a2 (b2a2), e14a2 (b3a2), and e19a2 fusion genes. The use of nested primers and sequential PCR reactions makes the technique extremely sensitive, capable of routine detection of one Ph-positive cell in 10^5 to 10^6 normal cells [26]. (See 'Distinct forms of BCR-ABL1 from alternative chromosome 22 breakpoints' above.)

Because RT-PCR is low-cost, sensitive, rapid, and not labor intensive, it is the diagnostic test of choice for Ph-positive leukemia. The data can be quantitated by including a competitive standard RNA in the reaction [27] or by monitoring the accumulation of product in real time using fluorescence [28]. This technique can be used to monitor response to treatment as well as to detect measurable residual disease (MRD; also referred to as minimal residual disease).

following allogeneic bone marrow transplantation [26,29,30]. (See "Overview of the treatment of chronic myeloid leukemia", section on 'Monitoring response'.)

Several features must be considered in the interpretation of RT-PCR data:

- There are many variables in the RT-PCR assay, including which internal standard to use, and how to compare results obtained in different laboratories. Several different internal reference standards are employed worldwide. The published definitions of molecular responses use *ABL1* as the reference gene, as this is employed by the majority of laboratories, including most in the United States. *GUSB* is used in some European laboratories, while *BCR* is used in Australia and Asia. Many clinical laboratories now use an international reference standard to report RT-PCR results on the International Scale (IS), which allows direct comparison of patient results between laboratories and to data from clinical trials [31]. It is preferable to obtain serial samples from individual patients at the same laboratory, if possible [32]. Although several studies have shown reasonable concordance and correlation ($r = 0.85$ to 9.0) between quantitative RT-PCR results obtained from bone marrow aspirates and peripheral blood, the majority of molecular response data from clinical trials are based on analysis of peripheral blood samples, so only blood should be used for serial monitoring.
- Whereas quantitative *BCR-ABL1* transcript levels on the IS vary widely at diagnosis, two studies document that the velocity of decline in transcripts or the "halving time" is a better measure of favorable early molecular response than an arbitrary value such as 10 percent at three months [33,34]. Because the *ABL1* standard produces unreliable results in samples with high *BCR-ABL1* transcript levels (eg, taken at or near diagnosis), an alternative reference standard such as *GUSB* or *BCR* is necessary for this analysis.
- Patients with rare fusions, such as e6a2 or b2a3, may not be detected with standard primer sets.
- Patients with 5' m-bcr breakpoints can sometimes exhibit both e13a2 (b2a2) and e14a2 (b3a2) transcripts, while M-bcr breakpoints can also produce e1a2 transcripts at lower levels, probably due to alternative splicing [35].
- *BCR-ABL1* fusion transcripts (M-bcr or m-bcr) can be detected at very low level [one cell in 10^8 to 10^9] in hematopoietic cells from some normal individuals; this defines the limits of useful sensitivity of RT-PCR for diagnosis of leukemia [34].
- Digital PCR, which amplifies single *BCR-ABL1* RT products and employs Poisson statistics to calculate the absolute number of *BCR-ABL1* transcripts in a sample, is one to two logs more

sensitive than standard quantitative RT-PCR, but clinical applications of this test have not yet been defined [36].

- DNA-based PCR methods, which utilize patient-specific primers to amplify the chromosomal breakpoint in genomic DNA, are about 1 log more sensitive than conventional RT-PCR but require additional steps to identify the individual genomic fusion sequences. Comparison of the two methods in patients receiving front-line treatment with imatinib demonstrated a more rapid decline in mRNA transcripts than with DNA in the first three months, suggesting that the initial rapid decline in transcripts is due to a reduction in leukemic cells with proportionally more transcripts per cell than at later times during therapy [37].

Southern blotting — Southern blotting uses DNA probes from the three bcr regions (M-, m- and μ -bcr) to detect rearrangements in genomic DNA from leukemic samples. This method can distinguish the three different principal *BCR-ABL1* gene fusions but is labor-intensive and has a sensitivity similar to cytogenetics.

Western blotting — Western blotting permits direct detection of the BCR-ABL1 protein using a specific monoclonal antibody against BCR or ABL1 [38]. This technique allows unequivocal identification of the specific form of BCR-ABL1 protein present, but has a low sensitivity, is labor intensive, and is not commonly available in clinical laboratories.

Type of BCR-ABL1 fusion may influence the clinical manifestations — The various types of *BCR-ABL1* fusion may be associated with distinct leukemia phenotypes.

p190 and p230 fusion proteins — p190 ^{BCR-ABL1} is found in about 80 percent of childhood and 50 percent of adult Ph-positive B-ALL, but is infrequently observed in CML [39]. A retrospective study of 1384 patients with CML by Western blot identified only five with p190 [40]. The presence of p190 in chronic phase CML is correlated with monocytosis and a low neutrophil/monocyte ratio in the peripheral blood [40,41]. When compared with other patients with CML, patients with the p190 fusion protein may have an inferior outcome when treated with tyrosine kinase inhibitors. A retrospective analysis of 14 patients with p190 reported a low response rate to imatinib therapy with frequent evolution into accelerated or blast phase disease [42].

Several patients with e19/a2 BCR-ABL1 fusions and p230 ^{BCR-ABL1} have been described with a disorder similar to classic CML but with mild clinical symptoms. These include lower peripheral blood leukocyte counts consisting principally of neutrophils, thrombocytosis, less severe splenomegaly, and delayed or absent transformation to blast crisis. It was proposed that patients with the e19/a2 fusion comprise a distinct clinical entity called neutrophilic CML or

chronic neutrophilic leukemia, with a much more benign clinical course than that associated with traditional p210^{BCR-ABL1} [15]. However, other patients with the e19/a2 fusion appear to have typical CML [43]. Further prospective studies are needed to determine if patients with p230^{BCR-ABL1} indeed have a distinct clinical course.

Site of breakpoint in M-bcr region — An initial study suggested that a breakpoint in the 5' region of M-bcr, with generation of the e13a2 (b2a2) form of BCR-ABL1, was associated with a longer duration of chronic phase than patients with 3' breakpoints and e14a2 (b3a2) fusions [44]. However, later prospective studies have not confirmed any significant correlation between M-bcr breakpoint location and disease outcome [45]. Patients with 3' M-bcr breakpoints and/or e14a2 (b3a2) BCR-ABL1 transcripts may exhibit higher platelet counts, although this is also controversial.

Acute lymphoblastic leukemia — Ph chromosome-positive B-ALL is heterogeneous at the molecular genetic level. While the majority of such patients exhibit m-bcr breakpoints and p190^{BCR-ABL1}, about one-half of adults and 10 percent of children have M-bcr breakpoints and the p210^{BCR-ABL1}. Many of the latter patients have persistence of the Ph chromosome after chemotherapy-induced hematologic remissions and have the Ph chromosome in myeloid cells and in myeloid colonies grown in vitro, suggesting that they represent cases of CML presenting in blast crisis after an unrecognized chronic phase.

In contrast, most ALL patients expressing p190^{BCR-ABL1} do not exhibit the additional cytogenetic abnormalities typical of CML blast crisis, lack the Ph chromosome in myeloid cells and colonies, and become Ph-negative in hematologic remission. These observations suggest that the Ph translocation occurred in a cell that is more restricted in its differentiation potential than a pluripotent stem cell, perhaps a committed B-lymphoid progenitor. This hypothesis is supported by studies of xenotransplantation of Ph-positive ALL cells into NOD-SCID mice, in which leukemia-initiating cells from patients with p190 positive ALL had a committed B-lymphoid progenitor phenotype [46]. (See "Classification, cytogenetics, and molecular genetics of acute lymphoblastic leukemia/lymphoma".)

However, some patients with p190 positive ALL show persistence of the Ph chromosome in remission and in myeloid cells, consistent with a multipotential cell of origin. This is supported by a report of five patients with p190 positive ALL in whom the Ph chromosome was detected by interphase FISH analysis in granulocytes in all of the patients, suggesting multilineage involvement [47]. It is possible that some or most p190 positive CML patients have rapid transition to lymphoid blast crisis and nearly always present as ALL. In a second study, xenotransplantation of Ph-positive ALL cells into NOD/SCID mice suggested that the leukemia-initiating cell has a primitive (CD34+CD38-) phenotype [48]. Hence, further studies are needed

to determine if molecular categorization of patients with Ph-positive ALL offers useful prognostic and therapeutic information.

Ph-negative or atypical CML — Some patients with clinical features of CML lack the Ph chromosome by cytogenetic analysis. This occurred in approximately 15 percent of patients in a large prospective study from the Medical Research Council [49]. In about half of such patients, a "variant translocation" is seen in which one or more chromosomes in addition to 9 and 22 are involved in the *BCR-ABL1* translocation [50,51]. Another subset of patients may be Ph-negative by karyotype but have evidence of *BCR-ABL1* gene fusion by metaphase or interphase FISH analysis or RT-PCR. Initial studies suggested that patients with these variant translocations may have a worse outcome with imatinib therapy than those with classic translocations [52,53]. However, subsequent analysis of 559 patients enrolled on prospective studies of imatinib reported that the 30 patients with variant translocations had similar response rates to those seen in patients with the classic Ph translocation [54]. In addition, the deletion of the derivative chromosome 9 did not appear to affect patient outcome.

However, about one-third of the group lacked molecular evidence of *BCR-ABL1* fusion. In general, these patients have distinct clinical features, including short survival, poor response to therapy, absence of basophilia, frequent thrombocytopenia, and may progress to increasing leukocytosis, organomegaly, extramedullary infiltrates, and marrow failure without a terminal phase of AML [55]. It is likely that most of these patients have a disease that is distinct from CML, most likely one of the myelodysplastic or MDS/MPN overlap syndromes. It is important to pursue a molecular diagnosis in such cases, as some of these patients have leukemias associated with other dysregulated tyrosine kinases, such as PDGFRB, while many cases of chronic neutrophilic leukemia and atypical CML are associated with activating mutations in the receptor for granulocyte colony-stimulating factor (*CSF3R*) [56]. Some of these patients respond clinically to inhibitors targeting these pathways. (See "Clinical manifestations, diagnosis, and classification of myelodysplastic syndromes (MDS)", section on 'MDS/MPN syndromes' and "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on "Atypical CML".)

INFORMATION FOR PATIENTS

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level and are best for patients who want in-depth information and are comfortable with some medical jargon.

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- Beyond the Basics topics (see "Patient education: Chronic myeloid leukemia (CML) in adults (Beyond the Basics)")
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SUMMARY

- Chronic myeloid leukemia (CML) is a clonal myeloproliferative neoplasm derived from an abnormal pluripotent stem cell that has acquired the BCR-ABL1 fusion gene. This fusion gene is the product of a balanced translocation between chromosomes 9 and 22, denoted t(9;22) (q34.1;q11.21), which juxtaposes a 5' segment of a breakpoint cluster region (*BCR*) at 22q11 and the 3' segment of the *ABL1* gene at 9q34, resulting in an abnormally small chromosome known as the Philadelphia chromosome (Ph). (See 'The Philadelphia chromosome' above.)
- Chromosome 22 is broken at one of four exons (e1, e13, e14, or e19) and this exon is joined with *ABL1* exon a2 to produce one of four possible transcript products: e1a2, e13a2, e14a2, or e19a2, corresponding to the three common variants of *BCR-ABL1* (figure 2) (see 'Distinct forms of BCR-ABL1 from alternative chromosome 22 breakpoints' above):
 - p210^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in *BCR* at either e13 or e14 to produce an e13a2 or e14a2 transcript which is translated into a 210 kilodalton (kD) protein. This variant is present in most patients with CML and one-third of those with Ph-positive B cell acute lymphoblastic leukemia (Ph+ B-ALL).
 - p190^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in the minor *BCR* region at e1 to produce an e1a2 transcript which is translated into a 190 kD protein. This variant is present in two-thirds of those with Ph+ B-ALL and a minority of patients with CML.
 - p230^{BCR-ABL1} — Created by the fusion of *ABL1* at a2 with a breakpoint in the mu *BCR* region at e19 to produce an e19a2 transcript which is translated into a 230 kD protein. This variant is seen in some patients with chronic neutrophilic leukemia.

- The World Health Organization (WHO) diagnostic criteria for CML require the detection of the Ph chromosome or its products, the BCR-ABL1 fusion mRNA and the BCR-ABL1 protein. This can be accomplished through conventional cytogenetic analysis (karyotyping), fluorescence in situ hybridization (FISH) analysis, or by reverse transcription polymerase chain reaction (RT-PCR). (See 'Detecting the Philadelphia chromosome or its products' above and "Clinical manifestations and diagnosis of chronic myeloid leukemia", section on 'Genetics'.)

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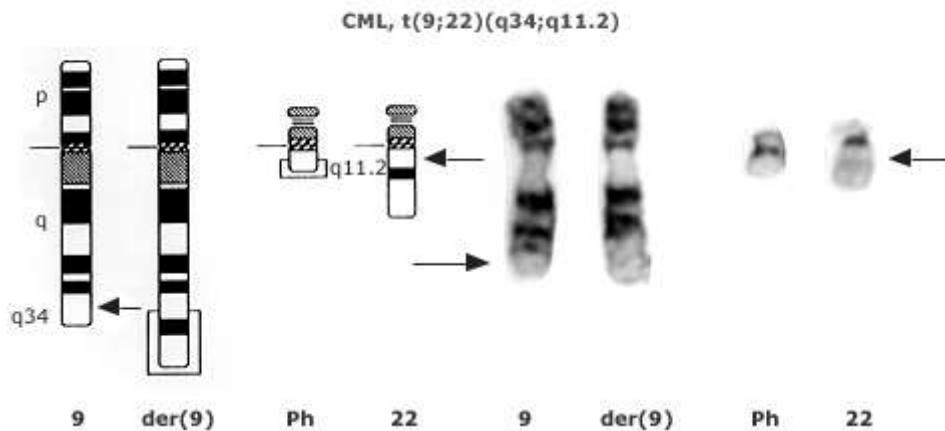
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GRAPHICS

The Philadelphia chromosome in chronic myeloid leukemia

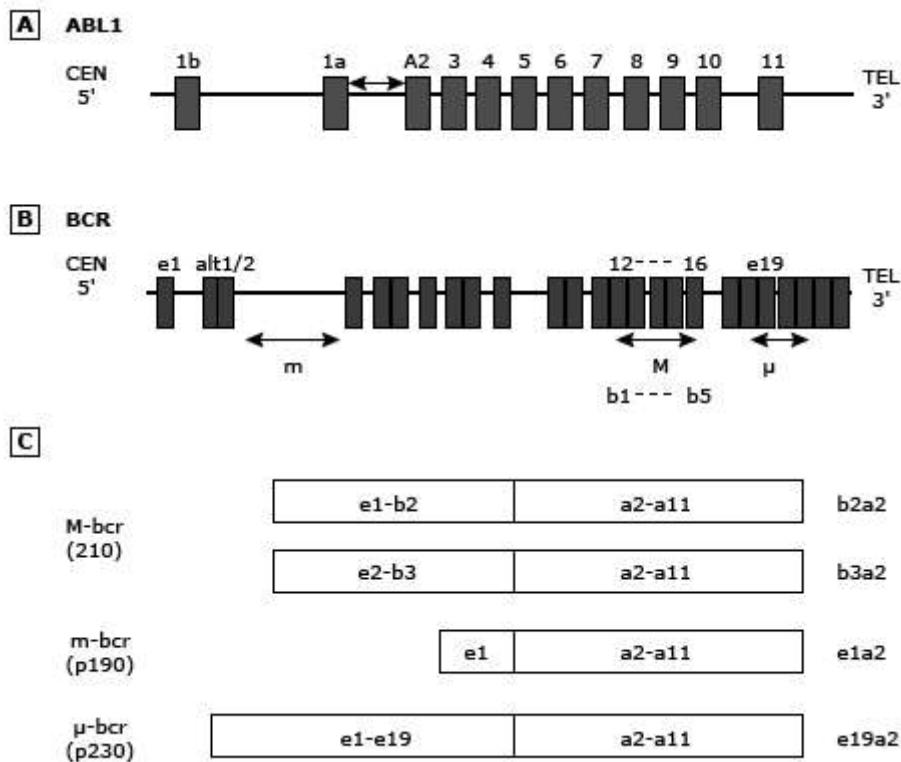


G-band ideograms (left) and partial karyotype (right) of the CML-associated chromosome translocation t(9;22)(q34;q11.2). Breakpoints are indicated with arrows on the normal chromosome homologs. Translocated segments are framed on the der(9) and Ph ideograms. The translocation results in a slightly longer chromosome 9 [der(9)] and a shorter chromosome 22 [der(22)], which is termed the Philadelphia (Ph) chromosome.

Courtesy of Athena Cherry, PhD.

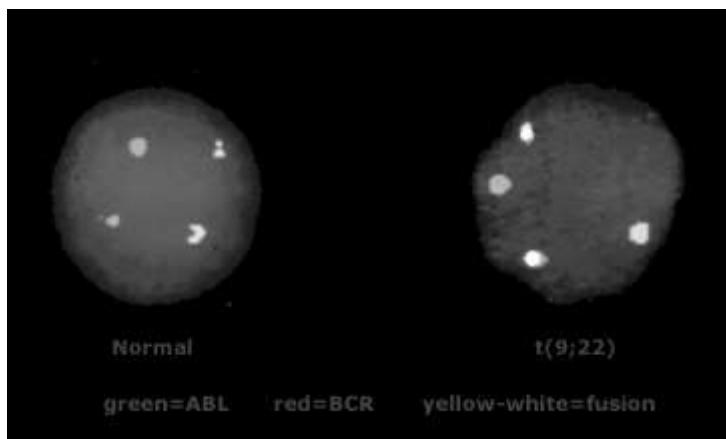
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ABL1 and BCR genes in chronic myeloid leukemia



A schematic representation of the ABL1 gene on chromosome 9 (A) and the BCR gene on chromosome 22 (B). All exons (red/blue boxes) have been scaled to the same size for clarity. Exon numbers are indicated above the coding sequence and the breakpoint cluster nomenclature is placed below the M-bcr (b1-b5). Introns are represented by the intervening lines. The various breakpoint regions are identified by double-headed arrows. The schematic fusion transcripts for the typical M-, m-, and μ -bcr are illustrated (C), while the translocation product is demonstrated on the right.

Interphase fluorescence in situ hybridization (FISH) images of normal and t(9;22) positive nuclei



The dual-color ABL (green) and BCR (red) probes span their respective breakpoint regions, producing two red and two green signals in a normal nucleus (on the left). In the t(9;22) cell (on the right), the single red and green signals correspond to the normal ABL and BCR genes, respectively, while the two yellow-white fusion signals correspond to the Ph chromosome and the reciprocal balanced translocation product (derivative chromosome 9).

Photo courtesy of Athena Cherry, PhD.

Graphic 73543 Version 1.0

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