

# Philadelphia chromosome

The **Philadelphia chromosome** or **Philadelphia translocation (Ph)** is a specific genetic abnormality in chromosome 22 of leukemia cancer cells (particularly chronic myeloid leukemia (CML) cells). This chromosome is defective and unusually short because of reciprocal translocation of genetic material between chromosome 9 and chromosome 22, and contains a fusion gene called *BCR-ABL1*. This gene is the *ABL1* gene of chromosome 9 juxtaposed onto the *BCR* gene of chromosome 22, coding for a hybrid protein: a tyrosine kinase signalling protein that is "always on", causing the cell to divide uncontrollably.<sup>[1]</sup>

The presence of this translocation is a highly sensitive test for CML, since all cases of CML are positive for *BCR-ABL1*.<sup>[2]</sup> (Some cases are confounded by either a cryptic translocation that is invisible on G-banded chromosome preparations, or a variant translocation involving another chromosome or chromosomes as well as the long arm of chromosomes 9 and 22. Other similar but truly Ph-negative conditions are considered CML-like myeloproliferative neoplasms.<sup>[3]</sup>) However, the presence of the Philadelphia (Ph) chromosome is not sufficiently specific to diagnose CML, since it is also found in acute lymphoblastic leukemia<sup>[4]</sup> (aka ALL, 25–30% of adult cases and 2–10% of pediatric cases) and occasionally in acute myelogenous leukemia (AML).

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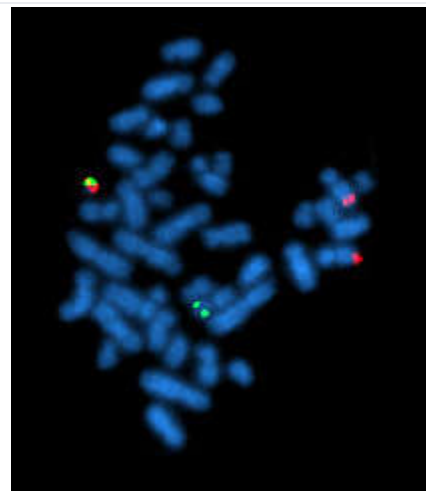
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## Molecular biology

The chromosomal defect in the Philadelphia chromosome is a translocation, in which parts of two chromosomes, 9 and

### Philadelphia chromosome



A metaphase cell positive for the *bcr/abl* rearrangement using FISH

### Classification and external resources

**Specialty** oncology

**ICD-10** C92.1 (<http://apps.who.int/classifications/icd10/browse/2016/en#/C92.1>)

**ICD-9-CM** 205.1 (<http://www.icd9data.com/getICD9Code.ashx?icd9=205.1>)

**ICD-O** 9875/3

**MeSH** D010677 ([https://www.nlm.nih.gov/cgi/mesh/2018/MB\\_cgi?field=uid&term=D010677](https://www.nlm.nih.gov/cgi/mesh/2018/MB_cgi?field=uid&term=D010677))

22, swap places. The result is that a fusion gene is created by juxtaposing the *ABL1* gene on chromosome 9 (region q34) to a part of the *BCR* (breakpoint cluster region) gene on chromosome 22 (region q11). This is a reciprocal translocation, creating an elongated chromosome 9 (termed a derivative chromosome, or *der 9*), and a truncated chromosome 22 (*the Philadelphia chromosome, 22q-*).<sup>[5][6]</sup> In agreement with the International System for Human Cytogenetic Nomenclature (ISCN), this chromosomal translocation is designated as t(9;22)(q34;q11). The symbol *ABL* is derived from Abelson, the name of a leukemia virus which carries a similar protein.

Translocation results in an oncogenic BCR-ABL gene fusion that can be found on the shorter derivative 22 chromosome. This gene encodes for a Bcr-abl fusion protein. Depending on the precise location of fusion, the molecular weight of this protein can range from 185 to 210 kDa. Consequently, bcr-abl is referred to as p210 or p185.

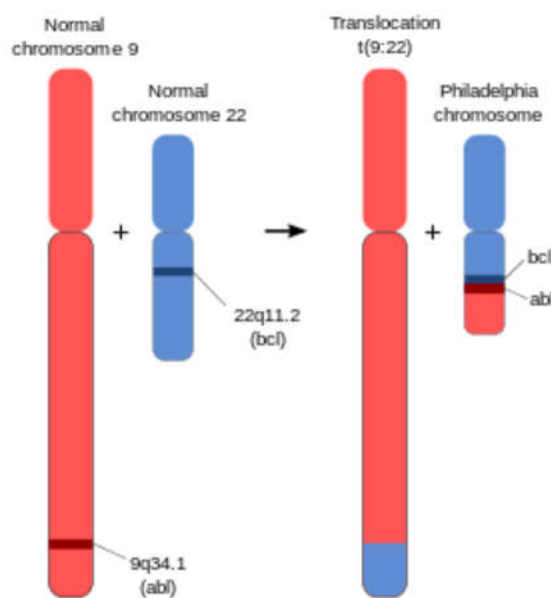
Three clinically important variants are the p190, p210, and p230 isoforms.<sup>[7]</sup> p190 is generally associated with acute lymphoblastic leukemia (ALL), while p210 is generally associated with chronic myeloid leukemia but can also be associated with ALL.<sup>[8]</sup> p230 is usually associated with chronic myelogenous leukemia associated with neutrophilia and thrombocytosis.<sup>[8]</sup> Additionally, the p190 isoform can also be expressed as a splice variant of p210.<sup>[9]</sup>

The Abl gene expresses a membrane-associated protein, a tyrosine kinase, and the BCR-Abl transcript is also translated into a tyrosine kinase. The activity of tyrosine kinases is typically regulated in an auto-inhibitory fashion, but the BCR-Abl fusion gene codes for a protein that is "always on" or continuously activated leading to unregulated cell division (i.e. cancer). This is due to the replacement of the myristoylated cap region, which when present induces a conformational change rendering the kinase domain inactive, with a truncated portion of the BCR protein.<sup>[10]</sup> Although the BCR region also expresses serine/threonine kinases, the tyrosine kinase function is very relevant for drug therapy. Tyrosine kinase inhibitors (such as imatinib and sunitinib) are important drugs against a variety of cancers including CML, renal cell carcinoma (RCC) and gastrointestinal stromal tumors (GISTs).

The fused *BCR-Abl* protein interacts with the interleukin-3 receptor beta(c) subunit. The ABL tyrosine kinase activity of *BCR-Abl* is elevated relative to wild-type ABL.<sup>[11]</sup> Since ABL activates a number of cell cycle-controlling proteins and enzymes, the result of the *BCR-Abl* fusion is to speed up cell division. Moreover, it inhibits DNA repair, causing genomic instability and potentially causing the feared blast crisis in CML.

## Nomenclature

The Philadelphia chromosome is designated **Ph (or Ph') chromosome** and designates the shortened chromosome 22. It arises from the translocation, which is termed **t(9;22)(q34.1;q11.2)**. This means there is a translocation between chromosome 9 and chromosome 22, with breaks happening in region (3), band (4), sub-band (1) of the long arm (q) of chromosome 9 and region (1), band (1), sub-band (2) of the long arm (q) of chromosome 22. Hence the



Schematic of the Philadelphia chromosome formation (bcl needs to be bcr)

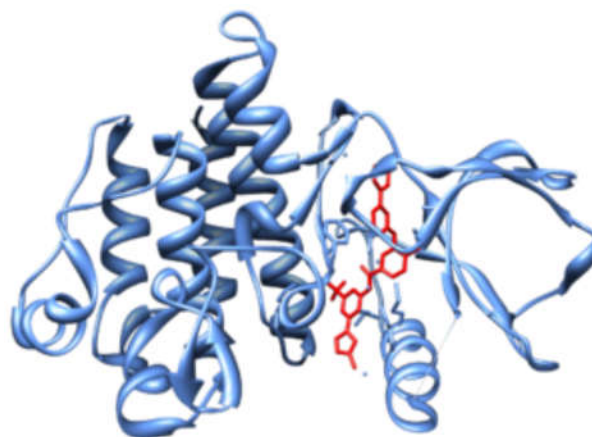
chromosome breakpoints are written as (9q34.1) and (22q11.2), respectively, using ISCN standards. Notation omitting the sub-bands is also commonly seen: **t(9;22)(q34;q11)**.

## Therapy

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### Tyrosine kinase inhibitors

In the late 1990s, STI-571 (imatinib, Gleevec/Glivec) was identified by the pharmaceutical company Novartis (then known as Ciba Geigy) in high-throughput screens for tyrosine kinase inhibitors. Subsequent clinical trials led by Dr. Brian J. Druker at Oregon Health & Science University in collaboration with Dr. Charles Sawyers and Dr. Moshe Talpaz demonstrated that STI-571 inhibits proliferation of BCR-ABL-expressing hematopoietic cells. Although it did not eradicate CML cells, it did greatly limit the growth of the tumor clone and decreased the risk of the feared "blast crisis". In 2000 Dr. John Kuriyan determined the mechanism by which STI-571 inhibits the Abl kinase domain.<sup>[12]</sup> It was marketed in 2001 by Novartis as **imatinib mesylate (Gleevec in the US, Glivec in Europe)**.



Crystal structure of Abl kinase domain (blue) in complex with 2nd generation tyrosine kinase inhibitor (TKI) nilotinib (red)

Other pharmacological inhibitors are being developed, which are more potent and/or are active against the emerging Gleevec/Glivec **resistant BCR-abl clones** in treated patients. The majority of these resistant clones are point-mutations in the kinase of BCR-abl. New inhibitors include dasatinib and nilotinib, which are significantly more potent than imatinib and may overcome resistance.

Axitinib, a drug used to treat renal cell carcinoma, has been shown to be effective at inhibiting the Abl kinase activity in patients with BCR-ABL1(T315I).<sup>[13]</sup> The T315I mutation in the fusion gene confers resistance to other tyrosine kinase inhibitors such as imatinib, however axitinib has been successfully been used to treat a patient with ALL carrying this mutation, as well as CML cells in culture.

Treatment of pediatric Ph+ ALL with a combination of standard chemotherapy and RTK inhibitors may result in remission, but the curative potential is unknown.

### Blood or marrow transplants

A potentially curative, but risky, option for pediatric Ph+ ALL or Ph+ CML is bone marrow transplant or cord blood transplant, but chemotherapy is favored by some for achieving first remission (CR1). For some, bone marrow transplant from a matched sibling donor or a matched, unrelated donor may be favored when remission is obtained.

Cord blood transplant is favored by some when a 10/10 bone marrow match is not available, and cord blood transplant may have some advantages, including a reduced incidence of graft-vs-host disease (GVHD), which is a common and significant complication of transplant. However, transplant with cord blood sometimes requires longer periods of time for engraftment, which may increase the potential for complications due to infection. Regardless of the type of transplant, transplant-related mortality and relapse are possible, and the rates may change as treatment protocols

improve. For second remission (CR2), if achieved, both chemotherapy and transplant options are possible, and many physicians prefer transplant.

## History

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The Philadelphia chromosome was first discovered and described in 1959 by [David Hungerford](#) from Fox Chase Cancer Center (then the Institute for Cancer Research) and [Peter Nowell](#) from the [University of Pennsylvania School of Medicine](#), and was named after the city in which both facilities are located.<sup>[1][14][15]</sup>

Hungerford was writing his doctoral thesis on chromosomes in a genetics lab at Fox Chase Cancer Center, and detected a tiny flaw in chromosomes from the blood cells of patients with a type of leukemia. It was the first genetic defect linked with a specific human cancer. Nowell was a pathologist at the University of Pennsylvania, studying leukemia cells under the microscope when he noticed cells in the act of dividing. To his surprise, their chromosomes—usually an indistinct tangle—were visible as separate structures.

Nowell searched for an expert on chromosomes in the area to work with and found Hungerford. While conducting his microscopic studies, Hungerford made the observation that certain leukemia cells had an abnormally short chromosome 22. The mutation became known as the Philadelphia chromosome.

In 1973, [Janet Rowley](#) at the [University of Chicago](#) identified the mechanism by which the Philadelphia chromosome arises as a translocation.<sup>[1][16][17]</sup>

## See also

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- [Chronic myelogenous leukemia](#)

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## External links

- Philadelphia+chromosome (https://meshb.nlm.nih.gov/record/ui?name=Philadelphia%20chromosome) at the US National Library of Medicine Medical Subject Headings (MeSH)
- bcr-abl+Fusion+Proteins (https://meshb.nlm.nih.gov/record/ui?name=bcr-abl%20Fusion%20Proteins) at the US National Library of Medicine Medical Subject Headings (MeSH)

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