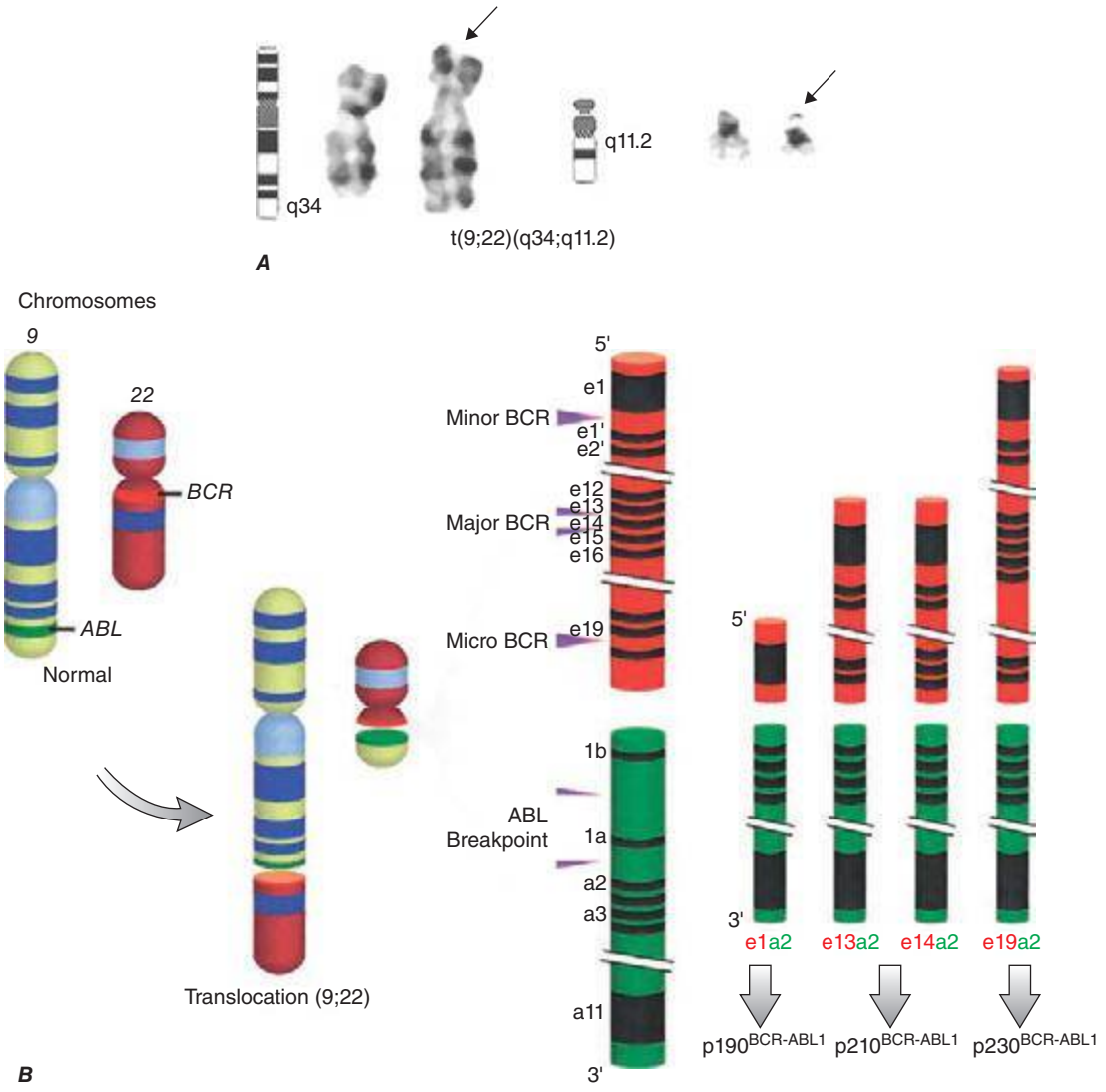

FIGURE 133-1 ***A.*** The Philadelphia (Ph) chromosome cytogenetic abnormality. ***B.*** Breakpoints in the long arms of chromosome 9 (*ABL* locus) and chromosome 22 (*BCR* regions) result in three different BCR-ABL oncoprotein messages, $p210^{BCR\text{-}ABL1}$ (most common message in chronic myeloid leukemia [CML]), $p190^{BCR\text{-}ABL1}$ (present in two-thirds of patients with Ph-positive acute lymphocytic leukemia; rare in CML), and $p230^{BCR\text{-}ABL1}$ (rare in CML and associated with an indolent course). *(© 2013 The University of Texas MD Anderson Cancer Center.)*

The cause of the *BCR-ABL1* molecular rearrangement is unknown. Molecular techniques that detect *BCR-ABL1* at a level of 1 in 10^8 identify this molecular abnormality in the blood of up to 25% of normal adults and 5% of infants, but 0% of cord blood samples. This suggests that *BCR-ABL1* is not sufficient to cause overt CML in the overwhelming majority of individuals in whom it occurs. Because CML develops in only 1.5 of 100,000 individuals annually, it is evident that additional molecular events or poor immune recognition of the rearranged cells are needed to cause overt CML.

CML is defined by the presence of *BCR-ABL1* abnormality in a patient with a myeloproliferative neoplasm. In some patients with a typical morphologic picture of CML, the Ph abnormality is not detectable by standard cytogenetic analysis, but fluorescence in situ hybridization (FISH) and molecular studies (polymerase chain reaction [PCR]) detect *BCR-ABL1*. These patients have a course similar to Ph-positive CML and respond to TKI therapy. Many of the remaining patients have atypical morphologic or clinical features and belong to other diagnostic groups, such as atypical CML or chronic myelomonocytic leukemia. These individuals do not respond to TKI therapy and have a poor prognosis with a median survival of about 2–3 years. Detection of mutations in the granulocyte colony-stimulating factor receptor (*CSF3R*) in chronic neutrophilic leukemia and in some cases of atypical CML and of mutations in *SETBP1* in atypical CML confirmed that they are distinct entities.

The mechanisms associated with the transition of CML from a chronic to accelerated-blastic phase are poorly understood. They are often associated with characteristic chromosomal abnormalities such as a double Ph, trisomy 8, isochromosome 17 or deletion of 17p (loss of *TP53*), 20q–, and others. Molecular events associated with transformation include mutations in *TP53*, retinoblastoma 1 (*RB1*), myeloid transcriptions factors like Runx1, and cell cycle regulators like p16. A plethora of other mutations or functional abnormalities have been implicated in blastic transformation, but no unifying theme has emerged other than that *BCR-ABL1* itself induces genetic instability that leads to the acquisition of additional mutations and eventually to blastic transformation. In this frame of thinking, one critical effect of TKIs is their ability to stabilize the CML genome, leading to a much reduced transformation rate. In particular, the previously observed sudden blastic transformations (i.e., abrupt transformation to blastic phase in a patient who had been in cytogenetic response) have become uncommon, occurring rarely in younger patients in the first 1–2 years of TKI therapy (usually sudden lymphoid blastic transformations). Sudden transformations beyond the third year of TKI therapy are rare in patients who continue on TKI therapy. Moreover, initial experience suggests that the course of CML has become significantly more indolent, even without cytogenetic responses, in patients on TKI-based therapy compared to previous experience with hydroxyurea/busulfan.