6.1 Introduction
Acute lymphoblastic leukemia (ALL) is characterized by distinctive morphologic, cytogenetic, and molecular genetic features, some of which have important clinical implications for both diagnosis and predicting response to specific treatment regimens, while the role of others is yet to be defined. This chapter will describe the cytogenetic and molecular aberrations in ALL.

6.2 Cytogenetic Aberrations
Cytogenetic aberrations can be structural, e.g., reciprocal and unbalanced translocations, deletions, dicentric chromosomes, or inversions; or numerical, e.g., gain of a whole chromosome (trisomy) or loss of a whole chromosome (monosomy). In many instances, molecular dissection of structural chromosome abnormalities, especially reciprocal translocations, identified specific genes associated with leukemogenesis. The most common structural cytogenetic aberrations and their affected genes are shown in Table 6.1.
6.3 Structural Aberrations

6.3.1 t(9;22)(q34;q11.2)

The t(9;22)(q34;q11.2) is the single most frequent chromosome abnormality in adult ALL, being detected in 11–34% of patients with ALL, and is associated with an unfavorable prognosis [1–9]. It rarely occurs in therapy-related ALL [10]. The reciprocal translocation between chromosomes 9 and 22 results in the head-to-tail fusion of variable numbers of 5′ breakpoint cluster region (BCR) exons on chromosome band 22q11.2 with the exon 2 of the ABL gene (named after the Abelson murine leukemia virus) located on chromosome band 9q34 [11]. The protein product of the fusion gene resulting from the t(9;22) plays a central role in the development of this form of ALL. Two main types of fusion proteins, p190BCR/ABL and p210BCR/ABL, each containing NH2-terminal domains of Bcr and COOH-terminal domains of Abl, are produced depending on the location of the breakpoint within the BCR gene. The p190BCR/ABL product contains the first exon of BCR and occurs in 50–78% of the ALL cases with t(9;22) [12–15]. The p210BCR/ABL product contains either exon 13 or exon 14 of BCR and is less frequent in ALL. However, p190BCR/ABL transcripts are frequently detected at a low level in p210BCR/ABL-positive ALL [16]. Clinically, there is no clear distinction between the two molecular variants of the disease [17–19], except for one report showing that the p210BCR/ABL product is associated with patients’ older age [20] and another report demonstrating a higher risk of relapse in p190BCR/ABL ALL following allogeneic transplantation [21]. Of interest, imatinib-containing treatment did not reveal any outcome difference between the two disease types [22].

Secondary chromosomal aberrations accompanying t(9;22) occur in 41–86% of adult ALL patients [18, 19, 23–26]. The most common additional aberrations in CALGB series [26] were, in order of decreasing frequency, +der(22)t(9;22), 9p rearrangements, hyperdiploidy (>50 chromosomes), +8, and −7. In this study, the presence of +der(22)(t(9;22)) was associated with a higher cumulative incidence of relapse while the presence of −7 as a sole secondary abnormality was associated with a lower complete remission rate [26].

At the molecular level, BCR/ABL has recently been shown to activate the Src kinases Lyn, Hck, and Fgr in ALL cells [27]. These kinases have not been activated in CML, suggesting a unique downstream signaling pathway in BCR/ABL-positive ALL. Further, application of DNA microarray gene expression profiling assay revealed that BCR/ABL-positive pediatric ALL is characterized by gene expression profiles distinct from other prognostically relevant leukemia subtypes [28]. These results were recently partially confirmed and validated in samples from adult ALL patients [29]. While adult BCR/ABL-positive ALL patients could be clearly distinguished from patients with T-cell ALL and patients with 11q23 rearrangements, their expression signatures were similar to those observed in a heterogeneous group of patients with B-precursor ALL who did not carry t(9;22) or t(11q23) chromosomal aberrations. It is hoped that microarray gene expression analyses will lead to identification of genes that can be targeted with individualized therapies and that this will increase response rates.

6.3.2 MLL Gene Rearrangements

The mixed lineage leukemia (MLL gene, also known as ALL-1, HTRX, or HRX) gene, located at chromosome band 11q23 [30], encodes a putative transcriptional regulator. It is involved in reciprocal translocations with several gene partners, localized on different chromo-