4. Structural abnormality t(12:21) in ALL

The following concerns the structural abnormality in ALL known as t(12;21). ALL commonly involves a chromosomal abnormality involving fusion of the TEL gene of chromosome 12 with the AML1 gene of chromosome 21, to produce a fusion gene. Expression of the fusion gene results in a fusion protein (175,176). The fusion product is named TEL-AML1 (also known as ETV6-RUNX1). TEL is also known as ETV6, while AML1 is also known as RUNX1. The chromosomal abnormality is named t(12;21), which refers to the fact that it is a translocation, and that the translocation involves chromosomes 12 and 21. The TEL-AML1 (ETV6/RUNX1) translocation appears to be a necessary first step in the development of ALL, but this mutation alone is not sufficient to cause leukemia (177,178).

In B-cell precursor acute lymphocytic leukemia (ALL), hyperdiploidy (more than 50 chromosomes) and TEL-AML1 fusion, which account for 25% and 23% of childhood cases but only 7% and 2% of adult cases, respectively, are associated with a favorable prognosis (179).

c. Cytogenetics for diagnosis and prediction – CML

Chronic myeloid leukemia formation is almost always dependent on an abnormal chromosome known as the Philadelphia chromosome. This genotype is known as *Ph positive*. The Philadephia chromosome is distinguished in that it encodes a mutant protein, that is, a fusion protein (BCR/ABL1) that is responsible for causing the cancer. The BCR/ABL1 fusion protein is essential for initiation, maintenance and progression of CML (180).

But in about 1% of patients with CML, the bone marrow cells appear to be *Ph negative*, although the BCR/ABL1 fusion gene still exists, where it may be located on chromosomes 22q11, 9q34 or even on a third chromosome (181). The failure to observe the Philadelphia chromosome in *Ph-negative* CML patients has been explained, by a scenario where a first translocation forms the Philadelphia chromosome, resulting in generation

[175] Burmeister T, Gökbuget N, Schwartz S, et al. Clinical features and prognostic implications of TCF3-PBX1 and ETV6-RUNX1 in adult acute lymphoblastic leukemia. *Haematologica*. 2010;95:241–246.

[176] Ford AM, Palmi C, Bueno C, et al. The TEL-AML1 leukemia fusion gene dysregulates the TGF-beta pathway in early B lineage progenitor cells. *J Clin Invest*. 2009;119:826–836.

[177] Wiemels JL, Hofmann J, Kang M, et al. Chromosome 12p deletions in TEL-AML1 childhood acute lymphoblastic leukemia are associated with retrotransposon elements and occur postnatally. *Cancer Res*. 2008;68:9935–9944.

[178] Metzler M, Mann G, Monschein U, et al. Minimal residual disease analysis in children with t(12;21)-positive acute lymphoblastic leukemia: comparison of Ig/TCR rearrangements and the genomic fusion gene. *Haematologica*. 2006;91:683–686.

[179] Pui C.-H. Impact of molecular profiling and cytogenetics in acute lymphoblastic leukemia. *Hematology*. 2005;10(suppl 1):176–177.

[180] Nacheva EP, Brazma D, Virgili A, et al. Deletions of immunoglobulin heavy chain and T cell receptor gene regions are uniquely associated with lymphoid blast transformation of chronic myeloid leukemia. *BMC Genomics*. 2010;11:41 [11 pages].

[181] Virgili A, Brazma D, Reid AG, et al. FISH mapping of Philadelphia negative BCR/ABL1 positive CML. *Mol Cytogenet*. 2008;1:14 [13 pages].