



**Karolinska
Institutet**

Institutionen för molekylär medicin och kirurgi

Molekylära studier av prognostiska och etiologiska faktorer vid barnleukemi

AKADEMISK AVHANDLING

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av

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood. It is caused by the somatic acquisition of genetic abnormalities and malignant transformation of immature lymphocytes in the bone marrow, most commonly of B-cell lineage. Chromosomal translocations are a hallmark of childhood ALL, constituting different subtypes of disease in terms of clinical characteristics and treatment outcomes. More than that, these gross chromosomal changes are often directly linked to specific disruptions at the molecular level through resulting fusion genes, aberrant transcriptional activation or associated structural and single nucleotide variants.

The aim of this thesis was to establish the frequency and prognostic impact associated with the chromosomal abnormality $\text{dic}(9;20)(\text{p}13.2;\text{q}11.2)$ in childhood B-cell precursor (BCP) ALL, and to better our understanding of the genetic basis underlying this disease. Thereby, we aimed to improve the diagnostics and risk-stratification in the context of existing anti-leukemic treatments, while potentially highlighting new rational strategies of therapy in $\text{dic}(9;20)$ and childhood ALL in general.

In **paper I** we found that the $\text{dic}(9;20)$ was present in almost five percent of BCP ALL cases, making it the third most common subgroup in the cohort. Furthermore, we showed that $\text{dic}(9;20)$ -positive cases treated on the NOPHO ALL-2000 protocol had a lower event-free survival than the most common subtypes of ALL. In **paper III**, we designed and validated a method for the detection of $\text{dic}(9;20)$ in a clinical setting using FISH. In **papers II and IV**, we characterized the genetic basis of disease in cases carrying the $\text{dic}(9;20)$, discovering first that homozygous deletions of tumor suppressor *CDKN2A* are present in almost all cases, but that the heterogeneity of the translocation breakpoints did not support the consistent formation of a fusion gene. Further, in **paper IV**, through the application of multiple genome-wide techniques, we presented a full spectrum of acquired structural and sequence level variation in $\text{dic}(9;20)$ -positive ALL, as well as the integrated analysis of DNA methylation, gene expression and anti-leukemic drug sensitivity. Together, these data revealed a genetic profile distinct from that of other ALL subtypes, not accounted for by individual fusion genes or single gene abnormalities alone. Importantly, we found evidence of altered expression of several key genes governing cell survival and programmed cell death, attributable to changes in promoter DNA methylation; some affecting the response to existing anti-leukemic agents, and others highlighting specific pathways that may be of value in developing new therapies.

Together, these studies add to our understanding of the clinical relevance and underlying biology of $\text{dic}(9;20)$ -positive BCP ALL and provide a basis for the rational exploration of new treatment options for children with this disease.