



# **Bruton's Tyrosine Kinase (Btk) and Nuclear Factor- $\kappa$ B (NF- $\kappa$ B) Genes Expression: Prognostic Biomarkers in Pediatric B-Cell Acute Lymphoblastic Leukemia**

Thesis

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## List of Abbreviations

<b>ABL1</b> .....	Abelson Murine Leukemia Viral Oncogene
<b>AF4</b> .....	ALL Fusion Gene on Chromosome 4
<b>AKT/m TOR</b> .....	Protein Kinase/Mammalian Target of Rapamycin
<b>ALL</b> .....	Acute Lymphoblastic Leukemia
<b>AML</b> .....	Acute Myeloid Leukemia
<b>AML1</b> .....	Acute Myeloid Leukemia 1
<b>AP</b> .....	Purinic/ pyrimidinic
<b>ARNT</b> .....	Aryl Hydrocarbon Nuclear Translocator
<b>ASCT</b> .....	Autologous Stem Cell Transplant
<b>ATP</b> .....	Adenosine Triphosphate
<b>BCP</b> .....	B-Cell Precursor
<b>Bcr</b> .....	Breakpoint Cluster Region
<b>BM</b> .....	Bone Marrow
<b>Btk</b> .....	Bruton's Tyrosine Kinase
<b>C</b> .....	Cytosine
<b>CBC</b> .....	Complete Blood Count
<b>CBF B</b> .....	Core Binding Factor B
<b>CD</b> .....	Cluster of Differentiation
<b>CNS</b> .....	Central Nervous System
<b>COG</b> .....	Children's Oncology Group
<b>CPTK</b> .....	Cytoplasmic PTK
<b>CR</b> .....	Complete Remission
<b>\\CRLF2</b> .....	Cytokine Receptor Like Factor 2
<b>CRLF2</b> .....	cytokine Receptor-Like Factor 2
<b>CSF</b> .....	Cerebrospinal Fluid

## List of Abbreviations

<b>CYP</b> .....	Cytochrome P450
<b>CYP1A1</b> .....	Cytochrome P450 A1
<b>DFS</b> .....	Disease Free Survival
<b>DNA</b> .....	Deoxyribonucleic Acid
<b>E2A, TCF3</b> .....	Early Region 2A, Transcription Factor 3
<b>EBV</b> .....	Epstein Barr Virus
<b>EDTA</b> .....	Ethylene Diamine Tetra-Acetic Acid
<b>EGIL</b> .....	European Group for Immunological Classification of Leukemia
<b>EPOR</b> .....	Erythropoietin Receptor
<b>ETV6</b> .....	Ets Variant 6
<b>FAB</b> .....	French-American-British
<b>FAD</b> .....	Flavin Adenine Dinucleotide
<b>FISH</b> .....	Fluorescence in Situ Hybridization
<b>FLT-3</b> .....	Fms-Like Tyrosine Kinase
<b>G</b> .....	Guanine
<b>GGR</b> .....	Global Genomic Repair
<b>GST</b> .....	Glutathione S-Transferase
<b>GSTP1</b> .....	Glutathione S-transferase Pi Family
<b>HIV</b> .....	Human Immunodeficiency Virus
<b>HOX</b> .....	Homebox Gene
<b>HTLV</b> .....	Human T. lymphotropic Virus
<b>iAMP21</b> .....	Intrachromosomal Amplification of hromosome 21
<b>IGH</b> .....	Immunoglobulin Heavy Chain Locus
<b>IKAROS (IKZF)</b> .....	Ikaros Family Zinc Finger Gene
<b>IL3</b> .....	Interlukins 3
<b>IL7</b> .....	Interlukins 7

## List of Abbreviations

<b>ITD</b>	Internal Tandem Duplications
<b>JAK2</b>	Janus Kinase2
<b>KMT2A</b>	Lysine Methyltransferase 2A-Protein Coding Gene
<b>LAIPs</b>	Leukemia - Associated Phenotypic Markers
<b>M-bcr</b>	Major Breakpoint Cluster Region
<b>MLL</b>	Mixed-Lineage-Leukemia
<b>MRD</b>	Minimal Residual Disease
<b>MYC</b>	Myelocytomatosis Viral Oncogen
<b>NADPH</b>	Nicotinamide Adenine Dinucleotide Phosphate
<b>ND</b>	Newly Diagnosed
<b>NER</b>	Nucleotide Excision Repair
<b>NF-<math>\kappa</math>B</b>	Nuclear Factor Kappa B
<b>NGS</b>	New Generation Sequencing
<b>NHEJ</b>	Non Homologous End Joining
<b>NOS</b>	Not Otherwise Specified
<b>OS</b>	Overall Survival
<b>PAH</b>	Poly Aromatic Hydrocarbons
<b>PAR1</b>	Pseudoautosomal Region 1
<b>PAS</b>	Periodic Acid Schiff
<b>PAX 5</b>	Paired Box 5
<b>PBX1</b>	Pre-B Cell Leukemia Transcription Factor 1
<b>PCR</b>	Polymerase Chain Reaction
<b>PDGFR</b>	Platelet-Derived Growth Factor Receptor
<b>Ph</b>	Philadelphia

## List of Abbreviations

<b>PI3K</b>	Phosphoinositide 3-Kinase
<b>POG</b>	Pediatric Oncology Group
<b>pre-B-ALL</b>	Precursor B-Acute Lymphoblastic Leukemia
<b>PTD</b>	Partial Tandem Replication
<b>PTKs</b>	Protein Tyrosine Kinases
<b>Q-RT PCR</b>	Quantitative Reverse Transcriptase Polymerase Chain Reaction
<b>RAS</b>	Family of Retrovirus-Associated DNA Sequences
<b>Ras/Raf/MEK</b>	Chain of Proteins in the Cell Communicating Signals
<b>RLT</b>	RPTK Receptor PTK
<b>ROS</b>	Reactive Oxygen Species
<b>RUNX1</b>	Runt-Related Transcription Factor 1
<b>SJCRH</b>	St. Jude Children's Research Hospital
<b>SNP</b>	Single Nucleotide Polymorphism
<b>STAT</b>	Signal Transducer and Activator of Transcription
<b>T</b>	Thymidine
<b>T-ALL</b>	T-acute Lymphoblastic Leukemia
<b>TCF3</b>	Transcription Factor 3 (E2A Immunoglobulins Enhancer Binding factors)
<b>TCR</b>	T Cell Receptor
<b>TdT</b>	Terminal Deoxy Nucleotidyl Transferase
<b>TEL</b>	Translocation-ETS-Leukemia
<b>TKIs</b>	Tyrosine Kinase Inhibitors



## List of Abbreviations

<b>TLRs</b>	.....Toll Like Receptors
<b>TLX1</b>	.....T-cell Leukemia Homebox1
<b>TLX3</b>	.....T-cell Leukemia Homebox3
<b>TP53</b>	.....Tumor Protein 53
<b>TSLPR</b>	.....Thymic Stromal Lymphopoietin Receptor
<b>UV</b>	.....Ultraviolet Rays
<b>VEGFR</b>	.....Vascular Endothelial Growth Factor Receptor
<b>WBC</b>	.....White Blood Cells
<b>WHO</b>	.....World Health Organization

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## INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant disorder of lymphoid progenitor cells characterized by diverse cytogenetic and molecular abnormalities. It affects both children and adults, with peak prevalence in children of 2 to 5 years old and adults older than 50 years (*Pui et al., 2008*). Risk-adapted chemotherapy can cure more than 80% of childhood cases, but still 20% to 30% of cases relapse, with the development of serious complications including death (*Pui, 2007*). Moreover, the outcome of adult ALL patients are much poorer than that of children (*Garza-Veloz et al., 2015*).

Deregulation in gene expression of several key cellular pathways has been suggested as a useful tool to define prognosis and identify novel therapeutic targets for ALL (*Yoho et al., 2002*). Advances in the understanding of the pathobiology of ALL proposed that drugs which specifically target the genetic defects of leukemia cells could revolutionize the management of this disease (*Pui et al., 2008*).

Bruton's tyrosine kinase (Btk), a member of the Tec family kinases, is a cytoplasmic protein expressed mainly in hematopoietic cells, except T cells (*Smith et al., 2011*). Btk is involved in B-cell antigen receptor (BCR) signaling (*Tao et al., 2016*), where gene mutation or loss of function