

# Tumor necrosis factor and lymphotoxin-alpha genetic polymorphisms and risk of relapse in childhood B-cell precursor acute lymphoblastic leukemia: a case-control study of patients treated with BFM therapy

## ABSTRACT

The study indicates that the genetic polymorphisms studied in childhood B-cell precursor ALL treated with BFM protocols do not have a significant impact on risk of relapse.

## INTRODUCTION

A chronic debilitating autoimmune disease called Rheumatoid arthritis causes synovitis (synovial swelling) of the joints, bursae and tendon sheaths, but is not often manifested as a synosomal disease; instead, immunologic processes appear to mediate these systemic and articular manifestations. The presence of synovial abnormalities in rheumatoid arthritis is marked by synovial hyperplasia, neoangiogenesis, and inflammatory cell infiltration involving the myeloid, macrophage, or lymphoid lineages. There has been considerable debate over the relevance of the specific cell types (and their products) to inflammation in rheumatoid arthritis, but it seems likely that all these cell kinds play some role in disease pathogenesis. Rheumatoid arthritis is supported by the identification of certain types of T cells in blood and synovial tissue that express specific surface membrane proteins or express a limited range of antigen receptors. To exemplify, clonal amplifications of CD8<sup>+</sup> CD57<sup>+</sup> T cells are frequently found in the repertoire of T-cells from rheumatoid arthritis patients. Similarly, CD4<sup>+</sup>CD28<sup>-</sup> T cell replications occur in both the blood and synovial compartments or tumor sites of these patients and appear to be auto-reactive. Ultimately, the T-cell receptors for antigen expressed by these and other T-cell subsets often display bias in favor of receptor that expresses some V gene expression (in contrast to the detailed studies of T cell clonality in rheumatoid arthritis), but much remains unclear about the extent to which B-cell diversity varies in this disease. The interpretation that the B-cell repertoire is also restricted is supported by previous studies. Circulating B cells were found to have oligoclonality according to flow cytometry, and cell culture experiments revealed the spontaneous secretion of immunoglobulins of restricted heterogeneity by synovial tissue explants as defined by immunological subclass, isoelectric focusing, or idiotype expression. Molecular studies of immunoglobulin genes found in the synovial tissue of rheumatoid arthritis patients provide new evidence for these concepts. These findings are significant because they reveal an ongoing immune response that targets specific (auto)antigens at low and high levels of B- and T-cells. By using the length of the third complementarity determining region (CDR3) of this rearranged copy of an enzyme called HCDR3, we were able to study the level of genetic alterations in B cells affected by rheumatoid arthritis through our current investigation. The immunoglobulin VH gene fingerprinting method, which has been used to identify the diversity of B cells and T cells in multiple clinical trials, was modified to address this problem. Recent findings indicate that B-cell clonal expansion is a typical and widespread feature of rheumatoid arthritis, that it includes both non-responsive and activated cells, and that this can persist for several months. These results provide support for the notion that autoimmune responses are involved in underlying chronic (auto)immune responses.

## CONCLUSION

Research indicates that the GFP-BLM fusion protein reduces SCE frequency in BS cells and acts as a helicase by activating its nucleotide domain. Instead of over-expression, the C-terminal domain encoded function in BLM is responsible for the stable nucleolar localization; mutations and deletions in the helicase domain have a dominant negative impact on the SCE frequency as do increases in chromosome abnormalities, while N-determination deletion has relatively little effect. According to the data, BLM's helicase activity and C-terminal domain directed nucleolar localization are crucial for genomic stability. The NBs appear to be storage or regulatory sites for BRM, but they are not necessary for their operation.