



بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون

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# Abstract

Immune thrombocytopenia (ITP) is an autoimmune illness characterized by an aberrant T cell response, which is supported by autoreactive B cell growth and differentiation. IL-18 expression has been linked to a number of autoimmune and inflammatory illnesses. IL18BP is a protein that binds IL-18 with high affinity, suggesting a potential mechanism for regulating IL-18 activity. Corticosteroids may play a significant role in reversing the IL-18-IL18BP ratio by upregulating IL18BP.

**Objective:** The aim was to study associations between IL-18 and two associated gene polymorphism sites -607 & -137 with incidence and response to therapy in patients with ITP. **Patients and Methods:** It is a case control study conducted on children and adolescents with ITP. A total of 55 patients with different stages of ITP (25 acute, 18 persistent & 12 chronic patients) were recruited with 30 age matched healthy controls. All patients were subjected to full history and physical examination. Laboratory investigations included serial blood counts, IL-18 and IL-18BP serum levels using enzyme linked immunosorbent assay (ELISA) and IL-18 gene polymorphisms using polymerase chain reaction (PCR). **Results:** At diagnosis the median platelet count was  $16 \times 10^9/L$  (range 2-79) & eventually increased to a median of  $190 \times 10^9/L$  after treatment. IL-18 level was significantly higher than that of control ( $P < 0.001$ ) & even after treatment. There was no significant difference between patient and control groups regarding the studied gene polymorphism sites -607 & -137. The mean IL-18 was still significantly elevated in all stages of ITP compared to control group & as well the drop after treatment. This was also observed in IL-18 BP which increased significantly after response to steroid therapy. However, it was observed that the decline in level of IL-18 as well as increment in IL-18 BP was the least in the patients tested during the acute phase. Mean IL-18 & IL-18 BP levels show no significant differences with gender, family history of ITP, mode of treatment or genotype. **Conclusion:** Among the studied IL-18 gene polymorphisms, no significant difference was detected among ITP patients or had a significant correlation with clinical or laboratory markers. Reversed IL-18/IL-18BP ratio is an important modulator in pathogenesis of ITP. Increasing levels of IL-18BP could have a significant role in treatment.

**Keywords:** Interleukin-18, Interleukin-18 Gene Polymorphisms; Immune Thrombocytopenia

# **Interleukin-18, Interleukin-18 Gene Polymorphisms and Interleukin-18 Binding Protein in Children and Adolescents with Immune Thrombocytopenia**

Thesis

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2022

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

قالوا

سببنا أنك لا تعلم لنا  
إلا ما علمتنا أنك أنت  
العليم العظيم

صدق الله العظيم

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# List of Abbreviations

| Abb.                  | Full term                                            |
|-----------------------|------------------------------------------------------|
| <i>ADP</i> .....      | <i>Adenosine diphosphate</i>                         |
| <i>AID</i> .....      | <i>Autoimmune disease</i>                            |
| <i>AIHA</i> .....     | <i>Autoimmune hemolytic anemia</i>                   |
| <i>AIM2</i> .....     | <i>Absence in melanoma 2</i>                         |
| <i>ALPS</i> .....     | <i>Autoimmune lymphoproliferative syndrome</i>       |
| <i>AML</i> .....      | <i>Acute myeloid leukemia</i>                        |
| <i>AMR</i> .....      | <i>Ashwell Morrell receptor</i>                      |
| <i>ANA</i> .....      | <i>Antinuclear antibody</i>                          |
| <i>Anti-D</i> .....   | <i>Anti-D immune globulin</i>                        |
| <i>AP-1</i> .....     | <i>Activator protein-1</i>                           |
| <i>APRIL</i> .....    | <i>A proliferation inducing ligand</i>               |
| <i>APS</i> .....      | <i>Antiphospholipid antibody syndrome</i>            |
| <i>ASH</i> .....      | <i>American Society of Hematology</i>                |
| <i>BAFF</i> .....     | <i>B cell activating factor</i>                      |
| <i>BCAP</i> .....     | <i>B-cell adapter for PI3K</i>                       |
| <i>BCG</i> .....      | <i>Bacillus Calmette–Guerin</i>                      |
| <i>Bcl6</i> .....     | <i>B cell lymphoma 6 protein</i>                     |
| <i>Breg</i> .....     | <i>Regulatory B cells</i>                            |
| <i>Btk</i> .....      | <i>Bruton’s tyrosine kinase</i>                      |
| <i>Caspases</i> ..... | <i>Cysteine-aspartic proteases</i>                   |
| <i>CBC</i> .....      | <i>Complete Blood Count</i>                          |
| <i>CD</i> .....       | <i>Cluster of differentiation molecule</i>           |
| <i>CMV</i> .....      | <i>Cytomegalovirus</i>                               |
| <i>CREB</i> .....     | <i>cAMP-responsive element binding protein</i>       |
| <i>CTLA-4</i> .....   | <i>Cytotoxic T- lymphocyte- associated protein 4</i> |
| <i>CTLs</i> .....     | <i>Cytotoxic T lymphocytes</i>                       |
| <i>CVID</i> .....     | <i>Common variable immunodeficiency</i>              |
| <i>CX3CR1</i> .....   | <i>CX3 chemokine receptor 1</i>                      |
| <i>DAT</i> .....      | <i>Direct antiglobulin test</i>                      |

# List of Abbreviations (Cont...)

| Abb.                      | Full term                                            |
|---------------------------|------------------------------------------------------|
| <i>DC</i> .....           | <i>Dendritic cells</i>                               |
| <i>DNA</i> .....          | <i>Deoxyribonucleic acid</i>                         |
| <i>dsDNA</i> .....        | <i>Double-stranded DNA</i>                           |
| <i>DSS</i> .....          | <i>Dextran sulphate sodium</i>                       |
| <i>EAE</i> .....          | <i>Experimental autoimmune encephalomyelitis</i>     |
| <i>EBV</i> .....          | <i>Epstein-Barr virus</i>                            |
| <i>EDTA</i> .....         | <i>Ethylenediaminetetraacetic acid</i>               |
| <i>ERK</i> .....          | <i>Extracellular Signal-regulated Kinase</i>         |
| <i>FasL</i> .....         | <i>Fas ligand</i>                                    |
| <i>FcγRs</i> .....        | <i>Fragment crystallizable gamma receptors</i>       |
| <i>FDA</i> .....          | <i>Food and drug administration</i>                  |
| <i>Fmol</i> .....         | <i>Femtomole</i>                                     |
| <i>Foxp3</i> .....        | <i>Forkhead box P3</i>                               |
| <i>g / dL</i> .....       | <i>Grams per decilitre</i>                           |
| <i>GIT</i> .....          | <i>Gastrointestinal tract</i>                        |
| <i>GP1Ib / IIIa</i> ..... | <i>Glycoprotein 2b / 3a</i>                          |
| <i>GPs</i> .....          | <i>Glycoproteins</i>                                 |
| <i>H. Pylori</i> .....    | <i>Helicobacter pylori</i>                           |
| <i>HBV</i> .....          | <i>Hepatitis B Virus</i>                             |
| <i>HCV</i> .....          | <i>Hepatitis C Virus</i>                             |
| <i>HIV</i> .....          | <i>Human immunodeficiency virus</i>                  |
| <i>HLA-B7</i> .....       | <i>Human leukocyte antigen B7</i>                    |
| <i>HLA-DR</i> .....       | <i>Human leucocyte antigen DR isotype</i>            |
| <i>HRQoL</i> .....        | <i>Health-related quality of life</i>                |
| <i>ICH</i> .....          | <i>Intracranial hemorrhage</i>                       |
| <i>ICOS</i> .....         | <i>Inducible costimulatory molecule</i>              |
| <i>ICSBP</i> .....        | <i>interferon consensus sequence binding protein</i> |
| <i>IDO</i> .....          | <i>Indoleamine 2, 3-dioxygenase</i>                  |

# List of Abbreviations *(Cont...)*

| Abb.                   | Full term                                   |
|------------------------|---------------------------------------------|
| <i>IFN-γ</i> .....     | <i>Interferon gamma</i>                     |
| <i>Ig</i> .....        | <i>Immunoglobulin</i>                       |
| <i>IGIF</i> .....      | <i>Interferon gamma inducing factor</i>     |
| <i>IKK</i> .....       | <i>IκB kinase</i>                           |
| <i>IL</i> .....        | <i>Interleukin</i>                          |
| <i>IL-18BP</i> .....   | <i>IL-18-binding protein</i>                |
| <i>IL-18R</i> .....    | <i>IL-18 receptor</i>                       |
| <i>IL-18Ra</i> .....   | <i>IL-18 receptor alpha</i>                 |
| <i>IL-18Rβ</i> .....   | <i>IL-18 receptor beta</i>                  |
| <i>IL-1RAcPL</i> ..... | <i>IL-1R accessory protein-like</i>         |
| <i>IL-1Rrp</i> .....   | <i>IL-1 receptor-related protein</i>        |
| <i>IPAF</i> .....      | <i>Ice protease-activating factor</i>       |
| <i>IRAK</i> .....      | <i>IL-1R-associated kinase</i>              |
| <i>ITP</i> .....       | <i>Immune thrombocytopenia</i>              |
| <i>IV</i> .....        | <i>Intravenous</i>                          |
| <i>IVIG</i> .....      | <i>Intravenous immunoglobulin</i>           |
| <i>IκB</i> .....       | <i>Inhibitor of κB</i>                      |
| <i>IWG</i> .....       | <i>International working group</i>          |
| <i>JNK</i> .....       | <i>c-jun N-terminal kinase</i>              |
| <i>K63-pUb</i> .....   | <i>K63-polyubiquitin chain</i>              |
| <i>kg</i> .....        | <i>Kilogram</i>                             |
| <i>KO</i> .....        | <i>Knockout</i>                             |
| <i>LPS</i> .....       | <i>Lipopolysaccharide</i>                   |
| <i>MAPK</i> .....      | <i>Mitogen-activated protein kinase</i>     |
| <i>MAS</i> .....       | <i>Macrophage activation syndrome</i>       |
| <i>M-CSF</i> .....     | <i>Macrophage colony stimulating factor</i> |
| <i>MDS</i> .....       | <i>Myelodysplastic syndrome</i>             |
| <i>mg</i> .....        | <i>Milligram</i>                            |
| <i>MHC</i> .....       | <i>Major histocompatibility complex</i>     |

# List of Abbreviations (*Cont...*)

| Abb.                    | Full term                                                                                                           |
|-------------------------|---------------------------------------------------------------------------------------------------------------------|
| <i>miRNAs</i> .....     | <i>MicroRNAs</i>                                                                                                    |
| <i>MKK</i> .....        | <i>MAPK kinase</i>                                                                                                  |
| <i>MKs</i> .....        | <i>Magakaryocytes</i>                                                                                               |
| <i>ml</i> .....         | <i>Milliliter</i>                                                                                                   |
| <i>moDC</i> .....       | <i>Monocyte-derived dendritic cells</i>                                                                             |
| <i>Mpl</i> .....        | <i>Myeloproliferative leukemia</i>                                                                                  |
| <i>mRNA</i> .....       | <i>Messenger Ribonucleic acid</i>                                                                                   |
| <i>MSC</i> .....        | <i>Mesenchymal stem cells</i>                                                                                       |
| <i>mTOR</i> .....       | <i>mammalian target of rapamycin</i>                                                                                |
| <i>MyD88</i> .....      | <i>Myeloid differentiation primary response 88</i>                                                                  |
| <i>NAIPs</i> .....      | <i>NOD apoptosis inhibitory proteins</i>                                                                            |
| <i>NEMO</i> .....       | <i>NF-<math>\kappa</math>B essential modulator</i>                                                                  |
| <i>NF</i> .....         | <i>Nuclear factor</i>                                                                                               |
| <i>NGS</i> .....        | <i>Next-generation sequencing</i>                                                                                   |
| <i>NK cells</i> .....   | <i>Nature killer cells</i>                                                                                          |
| <i>NLR</i> .....        | <i>Nucleotide-binding oligomerization domain<br/>(NOD)-like receptor</i>                                            |
| <i>NLRP3</i> .....      | <i>Nucleotide-binding oligomerization domain,<br/>Leucine Rich repeat and Pyrin domain<br/>containing protein 3</i> |
| <i>Ox-mit</i> .....     | <i>Oxydized mitochondria</i>                                                                                        |
| <i>PBMCs</i> .....      | <i>Peripheral blood mononuclear cells</i>                                                                           |
| <i>PC</i> .....         | <i>Plasma cells</i>                                                                                                 |
| <i>PD-1</i> .....       | <i>Programmed death-1</i>                                                                                           |
| <i>PEG-rHuMGDF</i> .... | <i>Pegylated recombinant human megakaryocyte<br/>growth and development factor</i>                                  |
| <i>PETIT</i> .....      | <i>Personal Evaluation of Transitions In<br/>Treatment</i>                                                          |
| <i>PI3K</i> .....       | <i>Phosphatidylinositol-3 kinase</i>                                                                                |

# List of Abbreviations *(Cont...)*

| Abb.                                 | Full term                                                 |
|--------------------------------------|-----------------------------------------------------------|
| <i>Platelet GP</i> .....             | <i>Platelet Glycoprotein</i>                              |
| <i>PRRs</i> .....                    | <i>Pattern-recognition receptors</i>                      |
| <i>PTT</i> .....                     | <i>Partial thromboplastin time</i>                        |
| <i>Rh(D)</i> .....                   | <i>Rhesus D antigen</i>                                   |
| <i>RNA</i> .....                     | <i>Ribonucleic acid</i>                                   |
| <i>ROC curve</i> .....               | <i>Receiver operating characteristic curve</i>            |
| <i>ROS</i> .....                     | <i>Reactive oxygen species</i>                            |
| <i>RTX</i> .....                     | <i>Rituximab</i>                                          |
| <i>SCID</i> .....                    | <i>Sever combined immunodeficiency</i>                    |
| <i>SLE</i> .....                     | <i>Systemic lupus erythematosus</i>                       |
| <i>SMOG</i> .....                    | <i>Skin, mucosa and organs gradation</i>                  |
| <i>SNPs</i> .....                    | <i>Single nucleotide polymorphisms</i>                    |
| <i>STAT4</i> .....                   | <i>Signal transducer and activator of transcription 4</i> |
| <i>SYK</i> .....                     | <i>Spleen tyrosine kinase</i>                             |
| <i>Tc1</i> .....                     | <i>T-Cytotoxic 1 cell</i>                                 |
| <i>Tc2</i> .....                     | <i>T-Cytotoxic 2 cell</i>                                 |
| <i>TCR</i> .....                     | <i>T-cell receptor</i>                                    |
| <i>TFH</i> .....                     | <i>T follicular helper cells</i>                          |
| <i>TGF-<math>\beta</math>1</i> ..... | <i>Transforming growth factor beta 1</i>                  |
| <i>Th1</i> .....                     | <i>Type 1 T helper cells</i>                              |
| <i>Th2</i> .....                     | <i>Type 2 T helper cells</i>                              |
| <i>TIMP3</i> .....                   | <i>Tissue inhibitor of metalloproteinase3</i>             |
| <i>TLR</i> .....                     | <i>Toll-like receptor</i>                                 |
| <i>TNF</i> .....                     | <i>Tumor necrosis factor</i>                              |
| <i>TPO</i> .....                     | <i>Thrombopoietin</i>                                     |
| <i>TPO-RAs</i> .....                 | <i>Thrombopoietin-receptor agonists</i>                   |
| <i>TRAF</i> .....                    | <i>Receptor-activated factor</i>                          |
| <i>TRAP</i> .....                    | <i>Thrombin receptor activating peptide</i>               |
| <i>Treg</i> .....                    | <i>regulatory T cells</i>                                 |

# List of Abbreviations (*Cont...*)

| Abb.                    | Full term                                                                       |
|-------------------------|---------------------------------------------------------------------------------|
| <i>Treg</i> .....       | <i>Regulatory T cells</i>                                                       |
| <i>TRIF</i> .....       | <i>TIR-domain-containing adapter-inducing<br/>interferon-<math>\beta</math></i> |
| <i>VCAM-1</i> .....     | <i>Vascular cell adhesion molecule-1</i>                                        |
| <i>VLA-4</i> .....      | <i>Very Late Antigen-4</i>                                                      |
| <i>XLA</i> .....        | <i>X-linked agammaglobulinemia</i>                                              |
| $\kappa$ <i>B</i> ..... | <i>Kappa B</i>                                                                  |

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