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Association Analysis of Kruppel like factor 1 (KLF1) And Secretion Associated Ras Related GTPase-1A (SAR1A) Genetic Polymorphisms with Hydroxyurea Response In β-Thalassemia Patients

Dr Muhammad Imran Qadeer
Sundas Foundation Hematology Center.

Abstract:

Haemoglobinopathies, characterized by abnormal hemoglobin levels, including β thalassemia are the most common inherited genetic blood disorders worldwide. Incidences of β thalassemia are increasing in Pakistan with more than 5000 cases being diagnosed every year. Management of β thalassemia requires regular blood transfusions and iron chelation therapy causing major healthcare burden on resource limited clinical settings in Pakistan. Hydroxyurea is the only cost-effective drug approved by Food and Drug Administration (FDA) to treat haemoglobinopathies. Mechanistically, hydroxyurea decreases the disease severity by regulating fetal haemoglobin (HbF). However, significant variability in response to hydroxyurea therapy exists among patients due to proposed genetic factors known to regulate gamma globin protein expression, necessitating the importance of better patients' stratification.

The current study reports association analysis of single nucleotide polymorphisms (SNPs) in KLF1 and SAR1A with hydroxyurea efficiency in patients with β thalassemia. To conduct this study 100, β thalassemia patients on hydroxyurea therapy and 100 patients without hydroxyurea therapy were recruited on the base of their basal HbF levels from different centers of Sundas Foundation across Punjab, Pakistan. Blood samples were collected from these patients following standard procedures. Whole blood DNA extraction was performed, KLF1 and SAR1A genes were amplified using polymerase chain reaction (PCR), followed by RFLP based genotyping to determine the association between SNPs (KLF1: rs2072597 and rs11085824, SAR1A: rs9971030 and rs3858169) of candidate genes and hydroxyurea response.

Findings of this study revealed no association between polymorphisms of KLF1 gene (rs2072597 A>G and rs11085824 A>G) (p=0.96 and p=0.75 respectively) and hydroxyurea therapeutic effectiveness. Moreover, association between HbF levels and genotypes of KLF1 polymorphisms rs2072597 A>G and rs11085824 A>G (p=0.45 and p=0.16 respectively) was not observed. Furthermore, association of SAR1A rs9971030:C>T and rs3858169: T>G polymorphisms with either hydroxyurea response (p= 0.96 and p= 0.26 respectively) or HbF levels (p= 0.13 and p= 0.34 respectively) was not found. Conversely, a strong association between physical activity (p=0.001) and hydroxyurea response was observed, suggesting that the hydroxyurea responders were physically active as compared to non-responders. In addition, significant association between rs9971030 genotypes with high HbF levels (p> 0.05) was observed. On the whole, the present study suggests that these genetic polymorphisms are not valuable pharmacogenomic predictors of hydroxyurea response in β thalassemia patients in Punjab, Pakistan.

Biography:

Dr Muhammad Imran Qadeer working at -Institute of Microbiology and Molecular Genetics, University of the Punjab, Lahore, Pakistan. Sundas Foundation hematological Center

dr.imran@sundas.org

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