HbH Disease in Bahrain: A Genotype-Phenotype Correlation Report

Nabeel Al Moamen, MPhil, PhD* Ahmed Thabet, MSc** Hema Newton, PhD** Hawra Khamis, BSc** Ameera Radhi, MD,FRCPA, FKSU*** Amani Al Hajeri, MD, CABFM, IBFM, MSc MG****

ABSTRACT

Objective: To uncover the molecular basis of hemoglobin H (HbH) disease in the population of Bahrain and correlate the underlying genotypes with phenotype presentations.

Design: A retrospective study covering more than 20 years of data collection and analysis for patients having alpha-thalassemia or relevant hematological phenotype manifestations.

Setting: Genetic Laboratory at Salmaniya Medical Complex.

Method: Molecular analysis was established by strip assay analysis targeting specific number of mutations which include the most common α−thalassemia mutations in Bahrain. Confirmation analysis was done by GAP-PCR analysis for the most common deletions ($-\alpha^{3.7}$ and $-\alpha^{4.2}$) and PCR-RFLP analysis for the most common point mutations ($\alpha^{TSaudi}\alpha$ and $\alpha^{Hph}\alpha$). Direct DNA sequencing was accomplished as a final confirmatory step for selected cases. Hematological phenotype analysis was accomplished by using an automated hematology analyzer whereas hemoglobin electrophoresis was accomplished with high performance liquid chromatography (HPLC) system.

Result: Our findings indicate that HbH disease in Bahrain can be broadly categorized into three levels according to the clinical and hematological phenotypes alongside with the underlying genotypes. The first and most severe type of HbH disease is caused by the homozygosity of the Saudi type polyadenylation (polyA) signal mutation (i.e., $\alpha^{TSaudi}\alpha/\alpha^{TSaudi}\alpha$); HBA2:c.*94A>G) showing an average level of Hb at 8.5±0.7 g/dL and severe hypochromic and microcytic RBCs with MCH and MCV levels of 18.1±0.5 pg and 60±3.5 fL, respectively. Some of these patients have infrequent blood transfusion and HbH inclusion bodies consistently found on the RBCs in peripheral blood smears after incubation with brilliant cresyl blue stain. The second type of HbH disease is attributed to the compound heterozygosity of the TSaudi haplotype and the pentanucleotide deletion (HBA2:c.95+2_95+6delTGAGG) in α2-globin gene (i.e., the genotype of ($\alpha^{TSaudi}\alpha/\alpha^{Hph}\alpha$)) with mean Hb level of 10±0.8 g/dL, and severe level of hypochromia and microcytic anemia at MCH and MCV levels of 18.3±0.9 fL and 58.7±2.6 pg, respectively. These patients rarely need blood transfusion and HbH inclusion bodies occasionally found in RBC peripheral blood smears. The third type, and mildest form of HbH disease in Bahrain, is caused by four different genotypes: ($-\alpha^{3.7}/\alpha^{TSaudi}\alpha$), ($-\alpha^{4.2}/\alpha^{TSaudi}\alpha$), ($-\alpha3.7/\alpha^{Hph}\alpha$), and ($\alpha^{Hph}\alpha/\alpha^{Hph}\alpha$),. These genotypes presented with an average of Hb levels at 10.8±1.0, 10.8±1.2, 10.5±1.6 and 11±1.3 g/dL, respectively. Rarely HbH inclusion bodies can be found in RBCs smears from these patients, and never need blood transfusion due to alpha genotype-related anemia.

Conclusion: This report summarizes the overall phenotype presentations of HbH disease in the population of Bahrain and their various underlying genotypes. This would help in better understanding of the genotype-phenotype correlations in these disorders and improve management and counselling for patients through a better understanding of the disease and relevant pathophysiology.

Keywords: Hemoglobin H, Alpha-Thalassemia, Salmaniya, Hypochromia

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* Head, Genetic Laboratory, Department of Pathology
Salmaniya Medical Complex
Bahrain
E-mail: NMohammed2@health.gov.bh

** Medical Technologist, Genetic Laboratory
Department of Pathology

*** Consultant hematopathologist and Transfusion Medicine
Department of Pathology

**** Consultant Clinical Geneticist