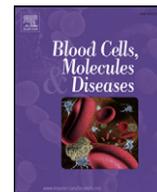




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journal homepage: www.elsevier.com/locate/bcmdThe spectrum of β -thalassemia mutations in Gaza Strip, PalestineMahmoud M. Sirdah^{a,*}, Jürgen Sievertsen^b, Mansour S. Al-Yazji^c, Issa S. Tarazi^d, Ramy M. Al-Haddad^d, Rolf D. Horstmann^b, Christian Timmann^b^a Biology Department, Al Azhar University-Gaza, Gaza, Palestine^b Department of Molecular Medicine, Bernhard Nocht Institute for Tropical Medicine, Hamburg, Germany^c Biology Department, Faculty of Applied Sciences, Al-Aqsa University-Gaza, Palestine^d Palestinian Thalassemia and Hemophilia Centre, Palestine Avenir Foundation, Gaza, Palestine

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ABSTRACT

Background: β -Thalassemia is a disorder caused by mutations at the hemoglobin β -gene (*HBB*) locus. Its most important manifestation, the major form, is characterized by severe hypochromic and hemolytic anemia and is inherited in an autosomal recessive mode. In Gaza Strip, Palestine 0.02% of the population has been identified as β -thalassemia major.

Design and methods: An assessment of mutations was performed in 49 transfusion dependent patients with β -thalassemia major and in 176 β -thalassemia carriers diagnosed with a mean erythrocyte cell volume (MCV) <80 fl and a proportion of HbA₂ $>3.5\%$. In addition 39 individuals suspicious for β -thalassemia carrier status due to a reduced MCV (<80 fl) but a normal HbA₂ were screened.

Results: By screening with three hybridization assays a proportion of 80% of the thalassemic chromosomes from patients and carriers was identified to carry five different mutations of the hemoglobin (Hb) β -gene. Subsequent DNA sequencing confirmed these and revealed further 9% of the chromosomes to be affected by other mutations. In addition six chromosomes from suspicious carriers were detected to carry β -thalassemia mutations. Of the 15 different *HBB* mutations identified the variant IVS-I-110 G>A was the most frequent mutation identified in 34% of the thalassemic chromosomes, followed by IVS-I-1 G>A, IVS-I-6 T>C, Codon 39 C>T, and Codon 37 G>A. Three novel *HBB* variants were discovered by direct sequencing of the gene: 5' UTR-50 (-/G), 5' UTR-43 C>T, and IVS-II-26 T>G.

Conclusions: The spectrum of *HBB* mutations described is of the Mediterranean type whereby the allele frequencies of the most common mutations differ from those, which were previously described for the population of the Gaza Strip and other Palestinian populations. The data presented may promote the introduction of molecular testing to the Palestinian premarital screening program for β -thalassemia in Gaza Strip, which will improve the screening protocol and genetic counseling in the future.

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Introduction

The thalassemias are hereditary anemias caused by mutations, which quantitatively affect the synthesis of human hemoglobin. They have been found in ethnicities originating from nearly every geographic location in the world, however, they are most common in those originating from tropic and subtropic regions of Africa and Asia and from the Mediterranean basin [1,2]. Thalassemias are classified according to which particular globin chain(s) is produced in a reduced amount. The main types which have now been defined are the α , β , $\delta\beta$, δ , and $\gamma\delta$ β -thalassemias. While α and β -thalassemias are the most common types of thalassemia however, β -thalassemia major and intermedia are the clinically most important types causing severe

transfusion dependent anemia with reduced life expectancy in the homozygous and compound heterozygous states [3–5]. Up-to-date, more than 400 different mutations have been reported and identified in the β globin gene, which are responsible for the development of the β -thalassemia (database HbVar, <http://globin.cse.psu.edu/hbvar/menu.html>) [6]. Moreover, a total of more than 700 genetic variants – which may or may not cause thalassemia – have been discovered in the β -globin gene region as documented by the National Center for Biotechnology Information (GenBank, <http://www.ncbi.nlm.nih.gov/snp/>).

In the Gaza Strip, Palestine, β thalassemia is recognized as a major health problem. More than 320 patients diagnosed with β -thalassemia major are currently being transfused and managed in local hospitals. The spectrum of mutations causing β -thalassemia in the Gaza Strip was not addressed comprehensively so far, the only sources with molecular genetics analyses were reported by Filon et al. in 1995 and Ayesb et al. in 2005 [7,8]. The study of Filon et al. included 39 transfusion dependent patients from the Gaza strip, no carriers were included in their study. The

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