



## Molecular heterogeneity of glucose-6-phosphate dehydrogenase deficiency in Gaza Strip Palestinians

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### ABSTRACT

**Background:** Glucose-6-phosphate dehydrogenase (G6PD) deficiency, affecting more than 500 million people worldwide, is one of the most common of inherited disorders. There are 186 G6PD mutations published, with mutational clustering within defined ethnic/racial groups. However comprehensive molecular characterization of ethnically associated G6PD mutants and their clinical implications are lacking.

**Design and methods:** Eighty unrelated Palestinian children hospitalized for hemolysis were studied. G6PD activity was determined by quantitative spectrophotometry and G6PD mutations were analyzed by sequencing of gDNA.

**Results:** 65 of 80 children (81%) had G6PD deficiency, accounting for most of the hemolytic disease in this age group. G6PD Mediterranean<sup>c.563T</sup>, African G6PD A-<sup>c.202A/c.376G</sup>, and G6PD Cairo<sup>c.404C</sup> were common with relative allele frequencies of 0.33 [1], 0.26, and 0.18 respectively. Two other variants were discovered, G6PD Beverly Hills<sup>c.1160A</sup> mutation, and a novel G6PD missense mutation c.536G>A (Ser179Asn), designated G6PD "Gaza". Three samples exhibited enzyme deficiency without detectable exonic or exon/intron boundary mutations.

**Conclusion:** G6PD deficiency accounts for the majority of diagnoses for hemolysis in Palestinian children (81%), providing support for newborn G6PD deficiency screening programs. We report unanticipated molecular heterogeneity of G6PD variants among Gaza Strip Palestinians greater than reported in neighboring Arab populations. We report a high proportion of affected children with G6PD Cairo, which was observed previously in only a single Egyptian, and a novel mutation G6PD "Gaza".

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### Introduction

Glucose-6-phosphate dehydrogenase (G6PD) is the first and rate-controlling enzyme in the pentose phosphate pathway, one of two enzymatic pathways required for the metabolism of glucose in red blood cells [2]. The pentose phosphate pathway generates nicotinamide adenine dinucleotide phosphate (NADPH), which maintains the reduced state of glutathione, allowing for reduction of peroxides and ensuring that reactive oxygen species (primarily H<sub>2</sub>O<sub>2</sub>) do not accumulate. High levels of reactive oxygen species can lead to increased

oxidation of hemoglobin that precipitates as Heinz bodies, as well as direct oxidation of the cell membrane that affects membrane integrity and leads to hemolysis [3,4]. As the pentose phosphate pathway is the only means red blood cells have to produce NADPH, any defect has significant effects on erythrocyte survival [5].

G6PD deficiency is one of the most common inherited red cell enzymopathic disorders; affecting more than 500 million people worldwide [6]. It is seen primarily in populations throughout the Mediterranean basin, Africa, Middle East and South Asia where *Plasmodium falciparum* malaria was endemic [4,7]. In humans, G6PD is located on the distal end of the X chromosome q-arm (Xq28), and consists of 13 exons. In red blood cells G6PD isoform b utilizes exons 2–13, encoding a 515 amino acid protein with a molecular weight of about 59 kDa [8]. Recent advances in molecular techniques have revealed at least 186 G6PD variants due to a variety of mutations throughout G6PD [9]. Many of these mutations occur at relatively high frequencies within specific populations, geographical locations and/or racial groups [10–12]. The absence

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