Tracing the Hidden Imprint of Hemoglobin O-Arab: A Nationwide Epidemiologic Insight"

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ABSTRACT

Hemoglobin O-Arab (HbO-Arab) is a rare β-globin variant characterized by the substitution of glutamic acid with lysine at position 121. Although typically asymptomatic in heterozygous form, its co-inheritance with other variants such as HbS or β-thalassemia can lead to clinically significant disease. Comprehensive population-level data on HbO-Arab in Saudi Arabia are scarce. A retrospective, population-based analysis of the PMSGC database was conducted from January 2011 to December 2018. Demographic, hematologic, and geographic data were extracted from the SEHA platform. Hemoglobin variants were identified using both high-performance liquid chromatography and capillary electrophoresis. Prevalence was calculated per 100,000 screened individuals. Among 1,871,184 screened individuals, 126 cases of HbO-Arab were identified, yielding a prevalence of 6.73 per 100,000 (95% CI: 5.60–7.99). Females represented 50.2% of cases. The Eastern Province had the highest regional prevalence (13.9 per 100,000), accounting for 42.9% of all cases. Mean hemoglobin concentration among carriers was 13.8 ± 2.0 g/dL, mean RBC count was 5.5 ± 0.7 × 10^{12}/L, mean MCV was 78.5 ± 7.0 fL, and mean MCH was 25.7 ± 2.9 pg. HbO-Arab is an uncommon hemoglobin variant in Saudi Arabia with marked regional clustering, particularly in the Eastern Province. These findings support the importance of accurate laboratory identification within national screening programs.

Keywords: Hemoglobin O Arab, HbO Arab, Saudi Arabia, Hemoglobinopathies, SEHA

INTRODUCTION

Hemoglobin O-Arab (HbO-Arab) is a structurally abnormal β-globin variant caused by a single point mutation at codon 121 of the β-globin gene on chromosome 11 (β121 Glu→Lys; HBB:c.364G>A)[1]. It was initially described in populations from the Middle East and North Africa and represents the predominant "O" hemoglobin variant reported among Arab communities, distinct from HbO-Padova and HbO-Indonesia[2]. On routine laboratory testing, HbO-Arab produces a slow-migrating fraction on alkaline electrophoresis and high-performance liquid chromatography (HPLC), frequently overlapping with the HbC or HbA_2 window, which may lead to diagnostic misclassification in high-throughput screening settings unless molecular confirmation is performed[3]. In the heterozygous state, HbO-Arab is typically hematologically silent or associated with mild microcytosis and borderline hypochromia[4]. However, co-inheritance with other β-globin disorders—most notably hemoglobin S—can result in a clinically significant sickling disorder that closely resembles homozygous sickle cell anemia[5].

Despite more than six decades since its initial description, the epidemiology of HbO-Arab remains incompletely characterized, particularly in regions with a high prevalence of hemoglobinopathies. The present study addresses this knowledge gap by utilizing data from the Saudi Premarital Screening and Genetic Counseling (PMSGC) program to determine the prevalence, hematologic characteristics, and geographic distribution of HbO-Arab across all administrative regions of Saudi Arabia. This nationwide analysis aims to provide robust epidemiologic data to support diagnostic accuracy, genetic counseling, and public health planning.

MATERIALS AND METHODS

Study Design: This study is a retrospective cross-sectional population-based analysis conducted using data from the Saudi Premarital Screening and Genetic Counseling (PMSGC) program. The analysis covered the period from January 2011 to December 2018 and included participants from all 13 administrative regions of Saudi Arabia. Demographic variables, including sex, age, and region of residence, along with laboratory findings, were obtained from the SEHA platform, a nationwide centralized electronic database.

Ethical approval was obtained from the Institutional Review Board of the Ministry of Health, Saudi Arabia (IRB approval number: 23-18E). As the study involved secondary analysis of anonymized data, the requirement for informed consent was waived.

Screening Analysis: Venous blood samples collected in EDTA tubes were obtained from authorized regional collection centers and analyzed at the designated central reference laboratories. Prior to testing, all specimens were stored at room temperature. A complete blood count (CBC) was performed for each sample using an automated hematology analyzer (Sysmex XE-2100; Sysmex Corporation, Kobe, Japan) to determine mean corpuscular hemoglobin (MCH) and mean corpuscular volume (MCV).

Detection of abnormal hemoglobin fractions was performed using capillary electrophoresis (CE) and high-performance liquid chromatography (HPLC), either independently or in combination. Hemoglobin separation was achieved with CAPILLARYS 2 (Sebia, France) and VARIANT II (Bio-Rad Laboratories, Hercules, CA, USA)

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Table1. The premarital screening program between 2011 and 2018 by gender in Saudi Arabia.

Structural Hb O-Arab	Total no. of cases	Mean ± SD % of the variant	Mean RBC±SD (x1012/L)	Mean HbG ±SD (g/dL)	Mean MCV±SD (fL)	Mean MCH±SD (pg)	Mean HbF (%)
Female	67	28.9±10.3	4.8±0.6	12.2±2.1	76.8±6.8	25.6±2.8	0.36
Male	59	30.1±11.2	6.2±0.9	15.4±2.1	80.4±7.2	25.8±3.0	0.48
Hb O-Arab	126	29.5±10.9	5.5±0.7	13.8±2.0	78.5±7.0	25.7±2.9	0.42

Table 2. The mean values and standard deviation of red cell indices and Hb F for the Hb O variant.

	Male	Female	Total
Number of Tested Individuals	9,31,099	9,40,085	18,71,184
Mean Age in years (±SD)	32.8 (±7)	27.5 (±7)	30.2±8.0
Abnormal tests	55,756 (49.5%)	56,862 (50.5%)	112,618 (6.0%)
HbO_{Arab} $HbO_{Arab}A$	59	67	126

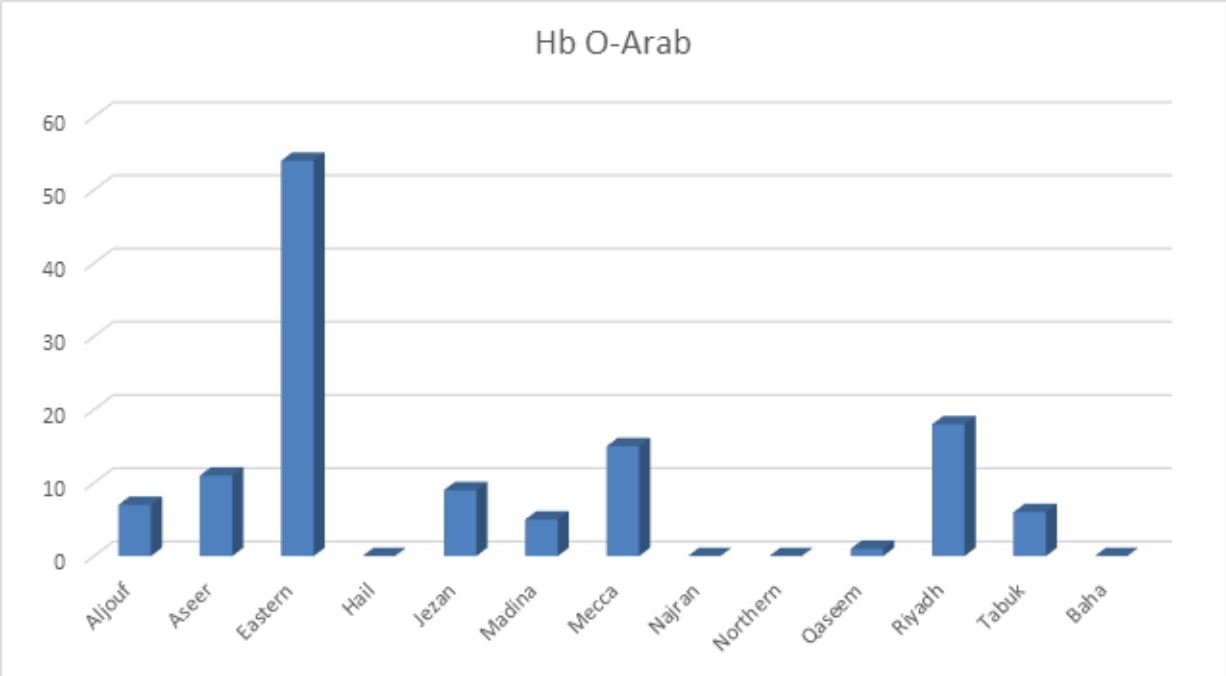

Figure 1. Hb-O Arab frequency in different regions of Saudi Arabia

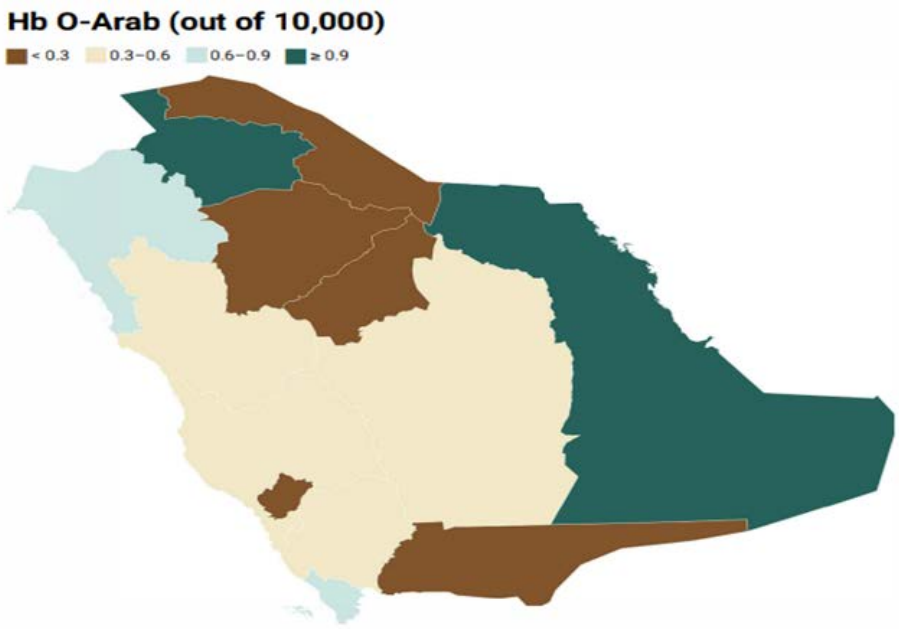

Figure 2. HbO-Arab out of 10000 Population in different regions

according to the manufacturers’ protocols. After approximately twelve hours of specimen storage, each sample was analyzed separately by both methods. Quantification of hemoglobin fractions and concentrations was performed using Sebia CAPILLARYS 2 software (Phoresis version 6.12).

Data Management and Statistical Analysis: Data were exported from SEHA platform, cleaned and validated prior to analysis. Statistical analyses were performed using MATLAB version 2023a (MathWorks Inc., Natick, MA, USA). Descriptive statistics were used to summarize demographic and hematologic variables. Continuous variables are presented as means ± standard deviations, while categorical variables are expressed as frequencies and percentages. The prevalence of HbO-Arab was calculated per 100,000 screened individuals, with 95% confidence intervals (CI) derived assuming a binomial distribution. Regional prevalence rates were calculated using the total number of screened individuals per region as the denominator. MATLAB was selected for its ability to efficiently manage large national datasets and perform reproducible statistical computations across multiple variables.

RESULT

Between January 2011 and December 2018, a total of 1,871,184 individuals were screened through the Saudi Premarital Screening and Genetic Counseling (PMSGC) program (Table 1). The cohort included 931,099 males (49.8%) and 940,085 females (50.2%), with a mean age of 30.2 ± 8.0 years. Hemoglobin O-Arab (HbO-Arab) was identified in 126 individuals, corresponding to an overall prevalence of 6.73 per 100,000 screened individuals (0.006%; 95% CI: 5.60–7.99). Of the identified carriers, 59 were male (46.8%) and 67 were female (53.2%), indicating a slight female predominance (Table 2). HbO-Arab identification was based on characteristic chromatographic and electrophoretic patterns detected by high-performance liquid chromatography and/or capillary electrophoresis within the PMSGC program. Routine molecular genetic confirmation was not performed as part of the national screening protocol.

The mean hemoglobin concentration among HbO-Arab carriers was 13.8 ± 2.0 g/dL, and the mean red blood cell count was 5.5 ± 0.7 × 10^{12}/L. Red cell indices were largely within near-normal ranges, with a mean corpuscular volume of 78.5 ± 7.0 fL and mean corpuscular hemoglobin of 25.7 ± 2.9 pg. The mean fetal hemoglobin (HbF) level was 0.42%.

Male carriers had a higher mean age (32.8 years) compared with female carriers (27.5 years). No clinically meaningful differences in hematologic indices were observed between males and females. Significant geographic variation in HbO-Arab prevalence was observed (Figure 1 and Figure 2). The Eastern Province accounted for the highest number of cases (n = 54; 42.9%), with a regional prevalence of approximately 13.9 per 100,000 individuals, exceeding the national average. Lower prevalences were observed in other regions: Riyadh (n = 18; 1.8 per 100,000), Makkah (n = 15; 1.5 per 100,000), Asir (n = 11; 1.1 per 100,000), Jazan (n = 9; 0.9 per 100,000), Al-Jouf (n = 7; 0.7 per 100,000), Tabuk (n = 6; 0.6 per 100,000), Madinah (n = 5; 0.5 per 100,000), and Qassim (n = 1; 0.1 per 100,000).

DISCUSSION

This nationwide analysis provides the most comprehensive epidemiologic assessment of Hemoglobin O-Arab (HbO-Arab) in Saudi Arabia to date. Using data from more than 1.8 million individuals screened through the PMSGC program, we demonstrate that HbO-Arab is a rare hemoglobin variant with pronounced regional clustering, particularly in the Eastern Province, where its prevalence was more than double the national average. The geographic concentration of HbO-Arab parallels the distribution of other hemoglobinopathies in Saudi Arabia, including sickle cell disease and β-thalassemia[6-8]. This pattern likely reflects shared historical, genetic, and sociocultural factors such as founder effects and high consanguinity rates. Unlike prior reports limited to small cohorts, the present study provides robust population-level data that allow accurate estimation of prevalence and regional variation[4,9,10].

Most identified carriers demonstrated near-normal hematologic indices, consistent with prior literature describing HbO-Arab as clinically silent in heterozygous form[4,10]. However, the clinical relevance of HbO-Arab lies in its potential interaction with other β-globin variants, particularly hemoglobin S, which may result in severe sickling phenotypes[5,11,12]. This underscores the importance of accurate identification within national screening programs, even for variants that appear benign in isolation[3].

A key contribution of this study is the confirmation that HbO-Arab remains under-recognized at the population level despite decades of screening for hemoglobinopathies (1–6). The overlap of HbO-Arab chromatographic patterns with HbC or HbA_2 highlights the need for continued laboratory vigilance and selective molecular confirmation, particularly in high-prevalence regions[3,4,16,17].

The primary strength of this study is its large, nationally representative sample derived from a mandatory premarital screening program, ensuring comprehensive geographic coverage and minimizing selection bias[6,11]. Standardized laboratory workflows across accredited centers further enhance data reliability.

Several limitations should be acknowledged. First, HbO-Arab identification was based on chromatographic and electrophoretic criteria without routine molecular confirmation, raising the possibility of misclassification[3]. Second, the PMSGC dataset does not capture longitudinal clinical outcomes or compound heterozygosity with other variants, limiting phenotype correlation[5,11,12]. Finally, age and sex distributions reflect a premarital population and may not be generalizable to pediatric or older cohorts[13].

These findings have direct implications for public health policy and genetic counseling in Saudi Arabia. Regional enrichment of HbO-Arab supports the need for geographically tailored screening strategies and heightened diagnostic awareness in high-prevalence areas[6,11]. Incorporating selective molecular confirmation for atypical hemoglobin profiles may improve diagnostic accuracy and counseling, particularly for couples at risk of clinically significant compound hemoglobinopathies. Continued optimization of national screening programs remains essential to reduce the burden of inherited blood disorders[11,14].

CONCLUSION

This nationwide analysis establishes that Hemoglobin O-Arab is a rare but regionally concentrated β-globin variant, predominantly observed in the Eastern Province. Although clinically silent in isolation, its interaction with HbS or β-thalassemia has major implications for screening and counseling. The findings underscore the importance of molecular diagnostic confirmation, regionalized genetic education, and continued expansion of national screening efforts to detect silent carriers and mitigate the burden of hemoglobinopathies in Saudi Arabia.

Authorship Contribution: GA conceived and designed the study, performed the data analysis, interpreted the results, and drafted the manuscript.

Potential Conflicts of Interest: None

Competing Interest: None

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