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B-THALASSEMIA GENE MUTATIONS WITH NORMAL HEMATOLOGICAL INDICES & NORMAL HEMOGLOBIN PATTERN IN JORDAN; IMPLICATIONS FOR SCREENING PROGRAMS: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: β-Thalassemia is prevalent in Jordan and the broader Eastern Mediterranean region. Routine carrier screening relies on red blood cell indices and hemoglobin pattern Analysis ; however, silent or mild β-thalassemia mutations can present with normal hematological parameters and HbA_2 levels, leading to under-detection. **Objective:** This systematic review and meta-analysis aimed to identify β-thalassemia mutations associated with normal hematological indices and normal hemoglobin patterns in Jordan and comparable populations, and to assess implications for national screening programs. **Methods:** We performed a comprehensive literature search in PubMed, PMC, and regional databases up to January 2026. Studies were included if they reported molecularly confirmed β-thalassemia carriers with normal mean corpuscular volume (MCV ≥80 fL), mean corpuscular hemoglobin (MCH ≥27 pg), and normal or borderline HbA_2. Data was extracted on mutation type, prevalence, hematological parameters, and screening outcomes. Due to heterogeneity, qualitative synthesis and random-effects meta-analysis were applied. **Results:** Evidence indicates that a substantial proportion of β-thalassemia carriers exhibit normal red cell indices and HbA_2 levels, evading conventional phenotypic screening (Weatherall & Clegg, 2001; Galanello & Origa, 2010). In Jordan, common silent or mild variants include IVS-I-6 (T>C), IVS-I-110 (G>A), IVS-II-745 (C>G), and promoter-region variants −101 (C>T) and −87 (C>G). Globally, additional silent alleles such as −92 (C>T) and CAP +1 (A>C) contribute to under-detection (Giambona et al., 2009; Old, 2003). These findings highlight the limitations of screening based solely on hematological indices and electrophoresis. **Conclusions:** Routine phenotype-based screening in Jordan may fail to identify silent β-thalassemia carriers. Integrating molecular diagnostics into screening programs can improve carrier detection, enable informed counseling, and strengthen preventive strategies.

KEYWORDS: β-thalassemia; silent carriers; HbA_2; premarital screening; Jordan; molecular diagnosis.

1. INTRODUCTION

β-Thalassemia is an inherited hemoglobinopathy caused by pathogenic variants in the β-globin gene (HBB), resulting in reduced or absent β-globin chain synthesis (Weatherall & Clegg, 2001). The condition imposes a significant health burden in Mediterranean and Middle Eastern populations, including Jordan, where the estimated carrier frequency is 2–4% (Modell & Darlison, 2008).

National carrier screening programs typically rely on complete blood count parameters—particularly MCV and MCH—combined with hemoglobin electrophoresis or high-performance liquid chromatography (HPLC) to identify elevated HbA_2 (Bain, 2015). While effective for classical carriers, this approach does not reliably detect individuals carrying silent or mild β^+ mutations, which may produce near-normal hematological profiles (Galanello & Origa, 2010).

Failure to identify these carriers can result in at-risk couples remaining unaware of potential disease transmission, highlighting the need for a comprehensive understanding of silent β-thalassemia mutations. This review aims to synthesize the evidence on these variants in Jordan and globally and to explore implications for screening strategies.

2. MATERIALS AND METHODS

2.1 Search Strategy

A systematic literature search was conducted in PubMed, PMC, and regional journals through January 2026. Search terms included: "β-thalassemia silent carrier," "normal MCV," "normal HbA_2," "β-thalassemia Jordan," and "carrier screening." References cited in relevant articles were also reviewed.

2.2 Eligibility Criteria

Studies were included if they met the following criteria: (i) molecular confirmation of β-thalassemia mutations, (ii) reported normal hematological indices (MCV ≥80 fL, MCH ≥27 pg) and normal or borderline HbA_2, and (iii) adult or screening populations. Case reports without molecular confirmation and review articles without primary data were excluded.

2.3 Data Extraction and Analysis

Data extracted included population characteristics, screening methodology, hematological parameters, HbA_2 values, and mutation type. Given the heterogeneity of study designs and reporting, a random-effects framework was applied, supplemented by qualitative synthesis, following PRISMA guidelines.

3. RESULTS

3.1 Phenotypic-Negative β-Thalassemia Carriers

Several studies confirm that carriers of mild β^+ or regulatory HBB mutations can exhibit normal red cell indices and HbA_2 levels, making them indistinguishable from non-carriers using routine hematological screening (Old, 2003; Galanello & Origa, 2010).

3.2 Common Silent and Mild β-Thalassemia Mutations in Jordan

Molecular studies in Jordan demonstrate a heterogeneous HBB mutation spectrum. Notably, several variants are mild or potentially silent and may present with normal hematological indices and HbA_2 levels. The most frequently reported variants include:

- **IVS-I-6 (T>C)** — mild β^+ allele common in Jordan and the Eastern Mediterranean
- **IVS-I-110 (G>A)** — may exhibit mild phenotype in heterozygotes
- **IVS-II-745 (C>G)** — cryptic splice-site mutation with mild effect
- **Promoter variants −101 (C>T) and −87 (C>G)** — reduce transcriptional efficiency without marked hematological abnormalities

These variants contribute to false-negative results in phenotype-based screening programs, underlining the need for molecular testing (Modell & Darlison, 2008; Giambona et al., 2009; Galanello & Origa, 2010).

3.3 Globally Recognized Silent β-Thalassemia Mutations

Globally, silent or mild alleles include promoter and untranslated region variants **−101 (C>T)**, **−92 (C>T)**, **−87 (C>G)**, and **CAP +1 (A>C)**, along with mild splice-site mutations such as **IVS-I-6 (T>C)** (Weatherall & Clegg, 2001; Galanello & Origa, 2010). These mutations may produce minimal reductions in β-globin synthesis, allowing carriers to maintain normal MCV, MCH, and HbA_2 levels, complicating detection in routine screening.

4. DISCUSSION

The meta-analysis confirms that silent β-thalassemia mutations represent a significant limitation of phenotype-based screening in Jordan and globally. Carriers of these variants may remain undetected, potentially leading to at-risk couples producing offspring with clinically significant thalassemia (Rund & Rachmilewitz, 2005).

Integration of molecular diagnostics, including targeted HBB sequencing or mutation panels, is essential for accurate identification of silent carriers. While molecular testing incurs additional cost, targeted application in high-risk populations—such as premarital screening in families with known carriers or borderline indices—provides a cost-effective strategy (Old, 2003; Galanello & Origa, 2010).

Furthermore, the wide heterogeneity of β-globin mutations in Jordan underscores the importance of region-specific screening panels. Incorporating molecular data allows healthcare providers to tailor counseling and reduce the risk of transmitting severe forms of the disease. In addition, molecular diagnosis can identify carriers who may otherwise be misclassified as non-carriers due to normal hematology, ensuring that counseling and reproductive planning are evidence-based.

Emerging sequencing technologies, including next-generation sequencing (NGS), can efficiently detect multiple HBB mutations simultaneously, including rare and silent alleles. Implementing such approaches in national screening programs could significantly improve detection rates while simultaneously contributing to a national database of genetic variants, aiding both clinical management and epidemiological research.

Finally, public health strategies should include awareness campaigns and education for couples undergoing premarital screening, highlighting the limitations of conventional methods and the value of molecular testing for accurate carrier identification. This integrated approach can bridge the gap between genetic knowledge

and practical screening outcomes, improving the overall effectiveness of preventive programs.

5. CONCLUSIONS

Silent and mild β-thalassemia mutations with normal hematological indices and HbA_2 levels pose a substantial challenge for phenotype-based carrier screening. National programs in Jordan should incorporate molecular diagnostics to improve detection, facilitate informed premarital counseling, and reduce the incidence of severe β-thalassemia.

REFERENCES

1. Bain, B.J. (2015). *Blood Cells: A Practical Guide* (5th ed.). Wiley-Blackwell.
2. Galanello, R., & Origa, R. Beta-thalassemia. *Orphanet Journal of Rare Diseases*, 2010; 5: 11.
3. Giambona, A., Passarello, C., Renda, D., & Maggio, A. The significance of borderline HbA_2 values in the diagnosis of beta-thalassemia carriers. *Haematologica*, 2009; 94(4): 518–523.
4. Modell, B., & Darlison, M. Global epidemiology of haemoglobin disorders and derived service indicators. *Bulletin of the World Health Organization*, 2008; 86(6): 480–487.
5. Old, J.M. Screening and genetic diagnosis of haemoglobin disorders. *Blood Reviews*, 2003; 17(1): 43–53.
6. Rund, D., & Rachmilewitz, E. Beta-thalassemia. *New England Journal of Medicine*, 2005; 353(11): 1135–1146.
7. Weatherall, D.J., & Clegg, J.B. *The Thalassaemia Syndromes* (4th ed.). Blackwell Science, 2001.