Consanguineous Marriages and Common Mutations in Iran: Two Key Points to Consider

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Article Info

doi10.61186/jambr.32.153.240
Received: 2024/10/16
Accepted: 2024/11/10
Published Online: 20 Nov 2022;

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Summary

Iran's diverse ethnic groups contribute to a unique genetic landscape, impacted by the high rate of consanguineous marriages and the prevalence of common mutation carriers. This leads to a higher incidence of autosomal recessive diseases, including congenital adrenal hyperplasia (CAH), non-syndromic hearing loss, beta-thalassemia, spinal muscular atrophy (SMA), and long QT syndrome (LQT). Common mutations causing these disorders vary across regions and ethnicities, emphasizing the need for tailored genetic screening programs. Advances in molecular diagnostics, like Next-Generation Sequencing and Whole Exome Sequencing, improve early detection and management of these conditions. National genetic screening programs have reduced beta-thalassemia incidence and are essential for informed reproductive decisions. These findings underscore the need for comprehensive public health strategies to tackle genetic disease burdens across Iran's communities.

Keywords: **Iran,Consanguinity,Congenital adrenal hyperplasia (CAH), Beta-thalassemia,Hearing loss,Genetic screening**

Introduction

Iran, with a population of over 85 million and a strategic location bridging Asia and Europe, hosts a diverse population composed of various ethnic subgroups including Persians, Azeris, Kurds, Arabs, Baloochis, Lurs, and Turkmens. This rich ethnic diversity, combined with a high prevalence of consanguineous and intragroup marriages—reported at over 30% in some regions—has created a unique genetic landscape, where certain monogenic diseases are notably more common. Consanguineous marriages, especially first-cousin marriages, play a significant role in the inheritance of autosomal recessive disorders **(1, 2)**. The high rates of consanguinity in Iran contribute to the increased frequency of several inherited diseases, including congenital adrenal hyperplasia (CAH), hearing loss, beta-thalassemia, spinal muscular atrophy (SMA), and long QT syndrome (LQT). In addition, for common mutations, due to the high prevalence of carriers in the population, there is a greater likelihood of these mutations occurring in a homozygous form, leading to an increased prevalence of the disease. Here are some examples of diseases that not only have common mutations in our population but also exhibit rare mutations in their genes, which become more apparent in consanguineous marriages.

CAH is primarily caused by mutations in the *CYP21A2* gene, which encodes the enzyme 21-hydroxylase. In Iranian populations, common mutations associated with 21-hydroxylase deficiency include p.V281L, IVSII-13A/C>G, and del8bp. These mutations lead to impaired cortisol and aldosterone synthesis, resulting in androgen excess and a variety of clinical manifestations **(3)**. Autosomal recessive non-syndromic hearing loss (ARNSHL) is prevalent in Iran due to the high frequency of consanguineous marriages. The *GJB2* gene, which encodes connexin 26, is the most commonly implicated gene. The 35delG mutation in the *GJB2* gene accounts for a significant portion of hereditary hearing loss cases in Iran, highlighting the importance of genetic screening in populations with high consanguinity rates **(4)**. Beta-thalassemia, one of the most prevalent genetic disorders in Iran, is caused by mutations in the *HBB* gene. Iran is part of the "thalassemia belt," where the carrier rate for beta-thalassemia ranges between 3-10%. Common mutations in the *HBB* gene in Iranian patients include IVSI-5G>C, IVSII-1G>A, and Codon 8 (-AA). These mutations lead to decreased or absent beta-globin chain production, resulting in the severe anemia characteristic of the disease **(5)**. SMA is an autosomal recessive neuromuscular disorder caused by mutations in the *SMN1* gene. Homozygous deletions of exon 7 in the *SMN1* gene are the most common mutation associated with SMA in Iranian patients. LQT, an inherited cardiac arrhythmia disorder, is often caused by mutations in genes encoding ion channels, particularly *KCNQ1*, *KCNH2*, and *SCN5A*. In Iran, *KCNQ1* mutations such as c.732_734delGG (p.Gly245Argfs*39 have been reported among patients with LQT syndrome **(6)**.

The prevalence of these mutations varies across different regions and ethnic groups in Iran. For example, the beta-thalassemia carrier rate is particularly high in the southern provinces, while certain mutations causing hearing loss and CAH are more common in the northwestern Azeri population. Consanguineous marriages, which significantly increase the likelihood of autosomal recessive disorders, play a major role in the distribution of these mutations. When parents share a recent common ancestor (founder effect), their offspring are more likely to inherit two copies of the same pathogenic variant, increasing the prevalence of recessive diseases such as hearing loss, beta-thalassemia, CAH, neurologic disorders **(3,5,7-9).**

The advent of molecular diagnostic techniques, such as Next-Generation Sequencing (NGS) and Whole Exome Sequencing (WES), has greatly enhanced the ability to diagnose genetic disorders in Iran. For diseases like CAH and beta-thalassemia, genetic testing not only confirms the diagnosis but also aids in identifying carriers, which is critical in populations with a high rate of consanguinity. For example, early detection of *CYP21A2* mutations in CAH can guide timely interventions such as glucocorticoid replacement therapy. In the case of LQT, genetic testing for mutations in *KCNQ1* or *SCN5A* is crucial for risk assessment and management, including beta-blocker therapy and lifestyle modifications[6]. Furthermore, national genetic screening programs, particularly for beta-thalassemia, have been implemented in Iran, with significant success in reducing the incidence of the disease. Pre-marital genetic screening has been mandatory in Iran since the 1990s for couples at risk of thalassemia, allowing for informed reproductive decisions.

At present, it is crucial to equip hospital centers with the necessary tools for genetic diagnoses, including methods for prenatal and preimplantation genetic testing. Until NGS technology becomes widely accessible in clinical settings, constructing mutation panels for common variants associated with these diseases can facilitate screening in the general population. This approach could help with the early identification of carriers of disease-causing mutations, potentially preventing the onset of numerous genetic disorders. Moreover, such screening can effectively inform individuals about genetic risks and support informed decision-making regarding marriage and family planning. Additionally, sufficient education on the genetic risks associated with consanguineous marriages, particularly the increased likelihood of homozygosity for rare mutations leading to genetic disorders, should be provided to couples considering such unions or incorporated into school curricula.

In conclusion, Iran's high rate of consanguineous marriages has led to an increased prevalence of various genetic disorders, including CAH, hearing loss, beta-thalassemia, SMA, and LQT syndrome. The distribution of common mutations varies across different ethnic subpopulations, reflecting the country's cultural and geographical diversity. Advances in genetic diagnostics have significantly improved the detection and management of these conditions, and ongoing public health initiatives aimed at expanding genetic screening and education are essential for reducing the burden of genetic diseases in Iran. Therefore, incorporating these factors is crucial in designing comprehensive screening programs and public health initiatives for our communities.

Acknowledgment

I acknowledge all staff of the Cardiogenetic Research Laboratory, Rajaie Cardiovascular Center for their assistance.

Funding sources

None to be stated.

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How to Cite This Article:

Nejat Mahdieh.Consanguineous Marriages and Common Mutations in Iran: Two Key Points to Consider J Adv Med Biomed Res. 2024; 32 (153): 107-8.

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