Persian Jewish Genetics

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In Jewish history, persecution and discrimination have often been enduring themes, propelling Jews across continents and oceans in a relentless search for refuge and acceptance. This tumultuous journey has given rise to a diverse array of Jewish communities, albeit united by a shared genetic heritage. Among these varied groups, Ashkenazi and Sephardic Jews have forged distinct identities: the former originating from Eastern and Central Europe, while the latter trace back to origins of Middle Eastern and Spanish ancestry [1, 2]. Yet within the Sephardic Jewry lies a subgroup with its own unique identity and genetic makeup — the Persian Jews. Shaped by historic migrations and centuries of geographic isolation, Persian Jews have been associated with a prevalence of genetic disorders that mirror the intricate interplay between heritage and health. Delving into the realm of Iranian Jewish Persian genetic diseases, the challenges and complexities faced by this vibrant community are highlighted. Among the many disorders prevalent among Persian Jews, some that stand out are β-thalassemia (β-thal), pseudocholinesterase deficiency E1, congenital hypoaldosteronism type 2, autoimmune polyendocrinopathy syndrome type 1, as well as hereditary inclusion body myopathy (HIBM), each illuminating the relationship between genetics and cultural heritage.

Iranian Jews date all the way back to biblical times when King Nebuchadnezzar conquered Babylon in the year 586 BCE. Jews from Judah, or modern-day Israel, were banished to Babylon a few times and only when Cyrus the Great came to power in 539 BCE were the Jews allowed to return to their homeland [1]. From here, some Jews returned to Israel, but some fled to Iran, setting up the foundation for a Persian Jewish community there. For centuries on end, the Persian Jews stayed together in Iran, practicing their religion and common beliefs in isolation. As time went on, larger communities developed in various cities in Iran, including Hamedan, Shiraz, Mashhad, and the capital city, Tehran.

In the ancient city of Hamadan, Iran, the Purim story unfolds, a narrative intertwined with the legendary bravery of Queen Esther and her uncle, Mordechai. Their courageous actions prevented Haman's sinister plot to annihilate the Jewish population of Iran and beyond. The festival of Purim commemorates this miraculous deliverance, celebrating the indomitable spirit and unwavering faith of Persian Jews in the face of grave danger. Remarkably, the events of the Purim story resonate with the genetic predispositions observed among Persian Jews today. Centuries of selective pressures, including persecution and geographic isolation, have left an indelible mark on the genetic landscape of this community, contributing to the prevalence of certain inherited diseases. Thus, while the saga of Purim stands as a testament to the resilience and fortitude of Persian Jewry, it also offers profound insights into their genetic challenges.

Following the establishment of the Jewish State of Israel in 1948, a surge of anti-Semitism swept across regions in the

The Middle East, compelling many Jews to seek refuge elsewhere. In Iran, a population of approximately 150,000 Jews faced the repercussions of this tumultuous period. Between 1948 and 1953, a significant number of Persian Jews opted to emigrate to Israel, resulting in a notable reduction of one-third in their community's size [3]. Under the rule of Shah Mohammad Reza Pahlavi, Persian Jews experienced a period of relative tranquility. The Shah was among the first monarchs to formally recognize Israel as an independent state, allowing Persian Jews to live freely within their communities. However, the 1979 Iranian Revolution abruptly disrupted this peaceful coexistence, led by Ayatollah Ruhollah Khomeini.

With the overthrow of the Shah, Khomeini imposed strict Islamic ideologies on Iran, including harsh treatment of religious minorities. Persian Jews were compelled to comply with these oppressive measures, prompting a mass exodus to the United States and Israel. As a result, only a small fraction of the Jewish population remained in Iran, constituting approximately 0.01% of the total population. This period marked a significant chapter in the history of Persian Jews, as they faced challenges and upheaval in their homeland.

It's important to recognize that within the cities of Iran, Persian Jews not only maintained a sense of isolation from non-Persians but also from non-Jewish/Muslim Persians. Consequently, there was a significant prevalence of intermarriage or consanguineous unions among Persian Jews residing in the same community. This practice, while culturally rooted, also exacerbated the risk of inheriting deleterious autosomal recessive disorders, posing serious reproductive health challenges. Genetic issues can arise from various sources, including alterations in DNA copy numbers, single gene mutations leading to simple and complex disorders, chromosome abnormalities, and epigenetic regulation disturbances [4]. These categories encompass a wide range of potential causes for genetic abnormalities.

Among the myriad of risks, one of the most prevalent genetic disorders is known as β-thalassemia (β-thal), a condition with grave implications. β-thalassemia is characterized by a deficiency in the production of beta-globin, a key component of hemoglobin - the molecule responsible for oxygen transport in red blood cells [5]. This deficiency stems from genetic inheritance and can lead to severe anemia and other complications. As evident, this disorder carries significant implications and is alarmingly common among consanguineous marriages, particularly within the Iranian Jewish community. This highlights the urgent need for increased awareness, genetic screening, and accessible healthcare resources to address the challenges faced by this population.

Another prevalent genetic disorder among Persian Jews is pseudocholinesterase deficiency, also known as butyrylcholinesterase deficiency (OMIM #177400), which follows an autosomal recessive inheritance pattern. This condition arises from mutations in the BCHE gene locus. Studies indicate that approximately

one in every ten Persian Jews carries a heterozygous mutation in this gene. Furthermore, the statistics reveal that one in every hundred couples will both carry the mutant gene, resulting in a 25% chance for each of their offspring to inherit two mutant genes and develop the disorder. Consequently, the overall incidence of this disease within the Persian Jewish population is estimated to be one in every 400 individuals [6].

Sadly, many affected individuals remain unaware of their condition until they encounter specific drugs that trigger symptoms. Ether-based anesthetics, such as succinylcholine, pose a particular risk as they are not effectively metabolized in individuals with pseudocholinesterase deficiency [6]. This failure to break down the drugs efficiently can lead to prolonged presence in the body, resulting in respiratory difficulties and muscle weakness.

Furthermore, Iranian Jews are commonly associated with the disorder, congenital hypoaldosteronism type 2, known as CMOII deficiency (OMIM #124080). This condition arises from insufficient levels of the corticosterone methyl oxidase II enzyme, encoded by the gene CYP11B2 located on chromosome 8q22. Manifestations of the disorder typically manifest in individuals homozygous for two-point mutations at separate allelic loci on the CYP11B2 gene. When two point mutations occur in a *cis* configuration, heterozygosity is indicated [6].

Research indicates that approximately one in every thirty Persian Jews carries a heterozygous mutation for CMOII deficiency. This statistic implies that approximately one in every nine hundred Persian Jewish couples carries the risk of their offspring inheriting the disorder. The ramifications of homozygosity for the mutation are profound, often leading to severe dehydration and shock shortly after birth [6]. Without timely intervention, newborns affected by this condition face life-threatening complications. Additionally, milder symptoms may include weakness, dizziness, irregular blood pressure, or cravings for salt.

An autosomal recessive disorder known as autoimmune polyendocrinopathy syndrome type 1 (OMIM #240300) has emerged as a prevalent concern within the Persian Jewish population. This condition is linked to mutations in the AIRE gene, which regulates autoimmune responses and facilitates fetal thymus "self" recognition. A single point mutation in this gene is observed in approximately one in every fifty Persian Jewish heterozygotes, suggesting that around one in every 2,500 Persian couples carries the risk of their offspring developing this disorder [6]. The manifestations of autoimmune polyendocrinopathy syndrome type 1 vary widely, depending on the glands affected by the autoimmune attack. Symptoms may include skin infections, anxiety, depression, infertility, and muscle weakness, among others. The diverse presentation sheds light on the complexity of this disorder and its profound impact on affected individuals' quality of life.

Hereditary inclusion body myopathy, HIBM (OMIM #600737), stands as another notable autosomal recessive disorder prevalent

among Persian Jews. Studies indicate that approximately one in every twenty individuals of Persian Jewish descent is affected by this debilitating condition. HIBM is characterized by a single-point mutation in the GNE gene [6]. The prevalence of HIBM among Persian Jews suggests that around one in every 400 couples within this community is at risk of conceiving a child with this disorder. The disease manifests with progressive muscle weakness, primarily affecting the arms and legs. Individuals typically experience difficulty walking by their 20s and 30s, with the condition steadily worsening over time until walking becomes impossible. The chronic and progressive nature of HIBM underscores the significant impact it has on affected individuals' daily lives and highlights the pressing need for further research and intervention strategies within the Persian Jewish community.

Given these complexities, it is crucial to emphasize the importance of genetic counseling, screening, and accessible healthcare resources to address the challenges faced by Persian Jews and mitigate the risks associated with these inherited disorders. By fostering awareness and providing support, we can strive to improve the health outcomes and well-being of individuals within the Persian Jewish community, ensuring a brighter and healthier future for generations to come.

As evident from the diverse origins of Jews — Ashkenazi, Sephardic, and their respective subgroups — it becomes clear that despite our varied backgrounds, we must rise above our differences and come together in our shared devotion to serving a higher power, *Hashem*. *Pirkei Avot* (6:6) emphasized the importance of empathizing with others' pain; we are reminded of our collective responsibility to support one another. This principle, encapsulated in the phrase "נושא בעל עם חבירו," calls upon us to prioritize inclusivity over exclusivity within our community. By embracing this compassion and solidarity, we can work towards realizing the vision of the holy Mashiach, transcending the divisions of animosity and hatred that may threaten our faith.

Through Persian Jewish genetic diseases, we uncover a profound interplay of history, culture, and health. From ancient migrations to modern-day challenges, Persian Jews have navigated a myriad of adversities, yet their resilience and tenacity shine through. The genetic heritage of this community, illuminated by disorders like β-thalassemia, pseudocholinesterase deficiency E1, congenital hypoaldosteronism type 2, autoimmune polyendocrinopathy syndrome type 1, and hereditary inclusion body myopathy (HIBM) displays the need for proactive measures. Genetic counseling, screening programs, and accessible healthcare resources emerge as crucial methods to address the unique challenges faced by Persian Jews. By fostering awareness and providing support, we can pave the way for a healthier future, where the burdens of inherited diseases are alleviated, and the vibrant legacy of the Persian Jewish community continues to thrive for generations to come.

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