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The Silent Threat: Unveiling the Genetics of Thalassaemia in India: A Comprehensive Review

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ABSTRACT Globally prevalent inherited disorders like beta-thalassaemia and sickle-cell anaemia are of great concern within the ethnic cultural diversity in India. The main objective is to review the underlying genetic aspects, especially the molecular basis of thalassaemia and to gain a comprehensive understanding of the genetic landscape of thalassaemia, highlighting the regional variations, diagnostic challenges and their implications for public health interventions. Databases like Google Scholar, Web of Science and Scopus were used to search for relevant papers that align with the study's objectives. This review collates knowledge available about the molecular genetics, prevalence, and diagnoses challenges of thalassaemia, especially South India. The review highlights the very high frequency of carriers of b-thalassaemia among tribal populations with the role consanguineous marriages play in increasing the prevalence of mutations. Besides, the review highlights the economic burden on families faced with thalassaemia, as thus far, treatment has been unaffordable for most. Gene therapy and molecular diagnosis hold promise for offering better hope for improvement in patients, while their access and affordability remain the most daunting challenge. Preventive strategies include comprehensive carrier screening, genetic counselling, and public health interventions aimed at reducing disease incidence and economic impact. The conclusion is drawn with implications for health policy and establishing new diagnostic technologies in resource-poor settings.

INTRODUCTION

Haemoglobinopathies are a prevalent kind of hereditary illness that occur globally. Pathogenic mutations in genes that regulate the synthesis of globin chains cause haemoglobinopathies, such as sickle cell disease. These mutations disturb the creation of functional haemoglobin molecules, which are essential for the transportation of oxygen in red blood cells (Pichamuthu et al. 2024).

Haemoglobinopathies, prevalent in Asia, tropical Africa, and the Mediterranean, have spread globally due to migration, making their epidemiological detection crucial, particularly in India, with its diverse population and geographic distribution (Kavitha A et al. 2023). India is a nation characterised by a multitude of faiths, which are further segregated into many castes. India has around 3,000 castes and 25,000 subcastes. Individuals in India adhere to their caste. Approximately 10.4 percent of the world's population still chooses consanguineous marriage (Bittles and Black 2010). In India, thalassaemia could be more economically efficient. The expense of providing optimal therapy for a single thalassaemic child amounts to around INR 1,500 per year. Therefore, the expenditure for 50,000 children would amount to around INR 620 crore. The exorbitant expense is unaffordable for the nation, and in India, this cost is projected to rise due to the birth of more children (Suresh Babu and Shantaram 2016).

A total of 24,287 people from 41 communities were examined in 14 investigations, resulting in the diagnosis of 973 individuals as beta-thalassaemia carriers. The combined frequency of individuals carrying the beta-thalassaemia gene in tribal societies was calculated to be 4.68 percent (Dharmarajan and Kar 2023). In India, around 80 β-thalassaemia mutations have been found and reported. The literature on ä-gene mutations is expanding. Mutations may cause a drop in HbA2 levels in persons carrying the β-thalassaemia gene, leading to misdiagnosis. About 15-20 metropolitan centres provide prenatal diagnostics (PND). If all β-thalassaemia patients get proper treatment, the expected yearly cost of care would increase from INR 30,000 million (USD 448 million) in 2016 to INR 55,000 million (USD 820 million) in 2026 (Colah et al. 2022). Several authors have identified 22 β-

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thalassaemia mutations in Indian individuals. Six mutations account for about 80 percent of â-thalassaemia cases in Indian populations. These are in codon 8-9 (+G), codon 15 (G-A), codon 41/42 (-TCTT), IVS I-1 (G-T), IVS I-5 (G-C), and a 619-bp deletion (Satpute et al. 2012).

Objectives

The main objective is to review the underlying genetic aspects, especially the molecular basis of thalassaemia and to gain a comprehensive understanding of the genetic landscape of thalassaemia, highlighting the regional variations, diagnostic challenges and their implications for public health interventions. The purpose of this study is to consolidate existing information on the genetic variants linked to thalassaemia in South India, emphasise the difficulties of genetic screening, and examine the consequences for patient care and public health policy.

Prevalence and Distribution

At present, there is no comprehensive national data available about the prevalence of individuals carrying the beta-thalassaemia gene. However, many studies have been conducted in specific regions and communities to assess the frequency of beta-thalassaemia carriers (Dharmarajan and Kar 2023). A report on the prevention and management of haemoglobinopathies has shown that in Tamil Nadu, the estimated prevalence of sickle cell anaemia ranges from 0 to 31 percent, while thalassaemia ranges from 1 to 3 percent. The report also highlights that these conditions are particularly common among the tribal communities (Ministry of Health and Family Welfare Government of India 2016).

India, with its rich tapestry of cultural backgrounds and diverse ethnicities, has a higher incidence of inherited disorders within specific communities. Through population screening, it has been discovered that specific communities are at a higher risk of â-thalassaemia, with a carrier status prevalence reaching as high as 17 percent (Yadav et al. 2022).

Haemoglobinopathies are very prevalent in the four southern states of India, namely Andhra Pradesh, Karnataka, Tamil Nadu and Kerala. These conditions are mostly seen in the Dravidian population, which is ethnically and culturally different from the Indo-European populations in the northern regions. The IVSI-5(GC) variant has a frequency of 67.9 percent, whereas the 619-bp deletion is seen in just 1.8 percent of cases. The second most frequent allele, accounting for 8.8 percent of cases, is codon 15 (GA). The Poly A site (TC) allele is the third most prevalent variant, accounting for 4.7 percent of occurrences (Sinha et al. 2009). The â-thalassaemia trait is the most prevalent haemoglobinopathy in the 0-10 year age range in South India, with an incidence of 22.61 percent (Kavitha A et al. 2023)

Thalassaemias and sickle cell diseases are major health concerns in India. According to the 2011 Census of India, a population of 1.21 billion individuals, including 8 percent of tribal tribes, has an average prevalence of â thalassaemia carriers of 3-4 percent, or 35-45 million carriers. The frequency is greater (4-17%) in certain ethnic groups (Madan et al. 2010; Office of the Registrar General and Census Commissioner 2011). Based on 27 million births in India, 32,400 newborns may have a significant haemoglobin problem (Colah et al. 2017). Regular and safe blood transfusions and iron chelation significantly improve the quality of life for patients with thalassaemia major in urban India. Multidisciplinary care is needed as they age. Although haemoglobinopathy patients now get free blood and iron chelators in many jurisdictions, testing, processing and leucodepletion still cost money. Therefore, most patients get suboptimal treatment. The only treatment available for patients with thalassaemia major is an allogeneic stem cell transplant. Good-risk patients have a more than a 90 percent likelihood of a successful transplant, whereas high-risk individuals have challenges (Mathews et al. 2014).

Genetic Diversity and Population Structure

Thalassaemia is common worldwide, but it is more prevalent in many countries, including India. The thalassaemia trait is divided into two main types of alpha and beta. Individuals with the beta thalassaemia trait have one normal beta globin gene and one altered gene that produces little or no beta globin. Alpha thalassaemia has different subtypes, with individuals lacking one alpha globin gene. When two alpha globin genes are missing, it is called the ‘alpha thalassaemia trait’. This can occur in two ways. The ‘cis’ alpha thalassaemia trait, where two genes are missing from the same chromosome, is most common in southeast Asian, Chinese and Mediterranean people. ‘Trans’ alpha

thalassaemia occurs when two genes are missing from different chromosomes. African Americans are most likely to have it (Li et al. 2022).

Thalassaemia syndromes are prevalent and include severe genetic disorders. They are native to a vast but distinct geographic region. Nevertheless, through migration, they are spreading over areas that were previously unaffected (Angastiniotis and Lobitz 2019). The disease is further exacerbated by its high mutation rate and the existence of genetic modifiers. β-thalassaemia is caused by over 300 identified mutations. The spectrum of mutations exhibits substantial variation across several geographical locations and community/ethnic groupings (Jaing et al. 2021). The early research on â-thalassaemia in Indian populations focused on overseas migrant groups. This research particularly aimed to identify thalassaemia variants in people from the states of Gujarat and Punjab, as well as in the Sindhi community, many of whom had roots in Pakistan (Sur and Chakravorty 2016).

People with thalassaemia intermedia have a wide range of genetic conditions, with most of them having homozygous β-thalassaemia and other genetic conditions like β-globin mutations, gene deletions, or XmnI polymorphism. People who have thalassaemia intermedia may have heterozygous β-thalassaemia with β-globin gene triplication or quadruplication, or very rarely they may have dominant β-thalassaemia. An intermediate phenotype results from the coexistence of a heterozygous thalassaemia condition with structural haemoglobin variations of HbE, HbS, or HbD. HPLC and mutation analyses categorise and distinguish these diseases (Jaing et al. 2021).

In the four states of Andhra Pradesh, Karnataka, Tamil Nadu and Kerala, the Dravidian population is ethnically and culturally distinct from the Indo-European populations of northern, central, and western India, which represents that the latter population flows into the Indian subcontinent (Ali et al. 2014). The genetic variety of the population in South India is a result of past migrations, the presence of several ethnic groupings, and the practice of endogamy. The presence of a significant amount of genetic diversity has resulted in a wide range of variations and kinds of thalassaemia mutations.

METHODOLOGY

The narrative review presented in this paper contains no element of primary data collection as it is based on secondary data. This primarily focuses on the current knowledge that covers the genetic basis of thalassaemia in India. Databases like PubMed, Scopus, ScienceDirect and Google Scholar were used. Some of the keywords—"thalassaemia," "genetic mutations," "haemoglobinopathies," "India," "diagnostic issues," and "public health interventions" were incorporated as part of this paper's literature search. Papers published in English between 2009 and 2024 were included. Papers were selected based on importance related to the genetic basis of thalassaemia, mutations found in the area under consideration, approaches to diagnosis in India, and implications for addressing thalassaemia prevention and control. The most recent papers were preferred based on the search produced in any of the topics found in this paper. Relevant data were extracted and analysed to identify regional patterns, diagnostic challenges, and implications for genetic counseling and public health interventions. Information was examined and assembled as a reasonably holistic picture of the molecular genetics pertaining to thalassaemia as a medical condition and public health challenges and implications.

RESULTS

Molecular Genetics of Thalassaemia

The mutation spectrum exhibits geographical and cultural variations. Regional mutation profiling is essential for the implementation of strategies such as genetic counselling and prenatal diagnostics. Mutations influence the extent of thalassaemia by being linked to various categories. If either the α or β globin genes are changed, they stop making globin chains, which stops red blood cells from forming fully. Diagnosing alpha thalassaemia poses a significant challenge, as 90 percent of cases in the Indian subcontinent persist as carriers (Hossain et al. 2017). India has a limited number of prevalent β-thalassaemia mutations. Several publications have reported twenty-two β-thalassaemia mutations in Indian individuals with β-thalassaemia. According to Sinha et al. (2009), about 80 percent of β-thalassaemia mutations in the Indian population are caused by six changes of codon 8-9 (+G), codon 15 (G-A), codon 41/42 (-TCTT), IVS I-1 (G-T), IVS I-5 (G-C), and a 619-bp deletion at the 32 end of the β-globin gene. A study was done in

Andhra Pradesh where DNA sequencing was used to investigate the prevalence of ß-thalassaemia in the population. Nine mutations were identified, with four accounting for 98 percent of positive cases. Two mutations, codon 8/9 (+G) and HbE (codon 26 G-A), were rare. During the diagnostic process, rare mutations were found. The codon 30 (G-C) mutation was confirmed, as well as the rare codon 5 (-CT) and IVS-II-837 (T-G) mutations (Bashyam et al. 2004).

In South Indian rural communities, it is common for families to practice endogamy by marrying within their own family, often between first cousins or uncle/niece relationships. Additionally, there is a significant prevalence of certain mutations in the community, with the IVS1+5G>T and c.47G>A mutations accounting for over 80 percent of all instances examined in this research. Consanguineous marriages significantly contribute to the high prevalence of this illness, and they are more common in the Muslim population compared to the Hindus (Sahoo et al. 2021).

A study in Karnataka used polymerase chain reaction and sequencing techniques to fully sequence the â-globin gene in 36 thalassaemia patients who were clinically discovered in the Karnataka area. The researchers have identified 11 different â-thalassaemia variants via the investigation. The most often seen mutations are IVSII-16 G>C, IVSI-5 G>C, IVSII-74 T>G, codon 3 (T>C), and the Poly A site (T>C). Furthermore, the researchers have recorded a new deletion at codon 6 (-CT) (HBB:c.16delCT) (Kulkarni et al. 2012).

The key mutations identified in South India include IVS-I-5 (G>C), Codon 15 (G>A), and 619 bp. Deletion modifier genes are genetic variations that alter the manifestation of a disease. In homozygous beta-thalassaemia, the main genetic factors that change the condition are genetic differences that may lessen the imbalance of globin chains. These modifiers have an impact on the severity of the illness, leading to a less severe type of thalassaemia. Beta-thalassaemia alleles that are silent or moderate cause a lot of beta-globin to be made. People also inherit alpha-thalassaemia and genetic factors that allow the production of gamma-globin chains (HbF) in adulthood (Galanello and Cao 1998), which are also factors that cause this condition.

In heterozygous beta-thalassaemia carriers, additional haemoglobinopathies, such as haemoglobin S, C and E, may induce clinically severe anaemia. Delta-beta-thalassaemia is clinically similar to beta-thalassaemia and results from the loss of neighbouring delta and beta genes. Delta-beta-thalassaemia has the same pathophysiology as beta-thalassaemia, but the delta chain is also damaged, and hence, HbA2 does not rise (Needs et al. 2024a).

Need for Screening

The only effective treatments for thalassaemia are gene therapy and bone marrow transplantation. Greece, Italy, Iran, Pakistan and Singapore have implemented measures such as public education, carrier screening, genetic counselling, prenatal diagnosis, and preimplantation diagnosis to prevent major births with thalassaemia (Gamage et al. 2023).

Thalassaemia can be classified into three different types of minor, intermedia, and major. β-Thalassaemia minor, also referred to as β-thalassaemia trait (BTT) or carrier state, occurs when a person has one normal and one mutated thalassaemia β globin chain. It is possible for a couple who both carry the β-thalassaemia gene to have a child with homozygous â-thalassaemia major, with a 25 percent chance (Needs et al. 2024b).

Researchers have extensively studied minor cases of thalassaemia and have developed four different methods for screening the condition. These screenings cover a wide range of populations, from prenatal and newborn to premarital and random total population. Screening for thalassaemia minor could help reduce the number of thalassaemia major cases. The screening process involves conducting a thorough haemogram and additional testing using the NESTROFT test if certain irregularities are found. Positive results on the NESTROFT test require further testing of HbA2 levels using HPLC or Hb electrophoresis. PCR and automated sequencing are effective methods for detecting mutations. Globally, over 180 distinct mutations have been discovered. The Mediterranean region has over 50 β-thalassaemia mutations, with specific mutations prevalent in different parts of the region (Riaz et al. 2022).

India's racial origin, tribal groups, and inbreeding in some communities make the population diverse. Population screening revealed that in certain communities in some parts of India, 17 percent of people are carriers of thalassaemia (Mohanty et al. 2022).

Complete hemogram can be used to detect different types of β-thalassaemia, including minor, major, and intermedia. β-thalassaemia major and intermedia typically show noticeable abnormalities in the body, while individuals with β-thalassaemia minor, also known as the carrier state, may appear normal, and detecting it can be challenging. Monitoring the levels of MCV, MCHC, and Hb during a complete hemogram is recommended (Needs et al. 2024c). People with MCV < 80 fl, MCH < 27 pg, and Hb < 15 for males and 14 for females need more tests, like NESTROFT and HbA, HbA2, and HbF levels, to find out if they have thalassaemia (Sorathiy et al. 2020). A thalassaemia screening scheme for schoolchildren and university students might help. Young people who know their carriers' status might be more careful when selecting spouses or obtaining genetic counselling before having children. For youth thalassaemia education and prevention campaigns to succeed, their knowledge, attitude, and practice (KAP) must be assessed. This is the first and biggest countrywide research of Indonesian youth KAP towards thalassaemia, and the researchers believe the results will impact future policy and preventative efforts (Wahidiyat et al. 2021).

Challenges in Genetic Screening

In many Mediterranean countries, screening and prenatal diagnosis have been successful in lowering the frequency of â-thalassaemia in newborns (Ali et al. 2021). The availability of family planning and prenatal screening for diagnosis, along with parents' refusal to have a therapeutic abortion due to cultural or religious beliefs, pose challenges to the prevention program (Andrews et al. 1994). Inadequate healthcare facilities and trained personnel in rural and underserved areas limit access to genetic testing and counselling. Endogamy and consanguineous marriages, prevalent in certain communities, not only increase the risk of thalassaemia but also pose challenges for genetic counselling due to cultural sensitivities.

Technological and Financial Constraints

Low income and high medical costs can affect a patient's quality of life if they have thalassaemia. First and foremost, having low financial standing can negatively impact one's ability to manage illnesses and obtain healthcare facilities and resources, as well as one's physical and mental health. Their quality of life and physical and mental health suffer as a result of their inability to afford the necessary treatment when it is needed (Hossain et al. 2023).

Cost of Testing

High costs associated with advanced genetic testing methods, such as next-generation sequencing (NGS), restrict their widespread use, particularly in resource-limited settings (Helmy et al. 2016).

Technical Expertise

A shortage of specialised laboratories and trained geneticists hamper the accurate diagnosis and management of thalassaemia.

DISCUSSION

Implications for Patient Care and Public Health Policy

Global campaigns draw attention to the need of policy frameworks guaranteeing universal access to iron-chelation treatments and gene therapies. In environments with limited resources especially, this is crucial (Thalassaemia International Federation 2024).

The family of an individual affected by thalassaemia feels burdened by the illness's protracted nature, the different types of treatment options available, the complications and deaths the condition causes, and the necessity of frequent trips to the hospital for vital blood tests and blood transfusions (Yousuf et al. 2022).

Since thalassaemia is a disease that mainly affects children, the lifelong treatment of iron chelation therapy and blood transfusions, especially the complications that follow transfusion, has left parents feeling psychologically distressed and frustrated. The physical changes brought on by the disease, which interfere with the children's everyday activities, further distress the parents. This distress starts when the disease is first identified in children (Mohamed et al. 2022).

The Thalassemia Bal Sewa Yojana (TBSY) program in India provides financial support for bone marrow transplants (BMT) reaching up to 10 lakh

(Press Information Bureau 2025). But the program finds it difficult to guarantee fair access given Ayushman Bharat's limited eligibility requirements. Among these criteria are income thresholds and ownership of basic appliance restrictions. Experts advise changing these criteria and combining thalassemia prevention with the national sickle cell elimination program to match the objectives the Prime Minister has announced for the year 2047 (Times of India 2024).

Clinical Management

- Personalised Medicine: Understanding the specific genetic mutations prevalent in South India can inform personalised treatment strategies, including targeted gene therapies and tailored management plans.
- Early Diagnosis and Intervention: Comprehensive carrier screening and prenatal diagnosis can significantly reduce the incidence of severe thalassaemia, improving patient outcomes and quality of life.

Public Health Strategies

The World Health Organisation (WHO 2024) claims that national initiatives combining prenatal genetic testing with community education have helped to lower the thalassemia incidence in areas with high frequency. On the other hand, the low level of knowledge of tribal people emphasizes the need of culturally customized screening campaigns (Kansal 2024).

Free blood transfusions, counseling, and partnerships with hospitals such as Rainbow Children's Hospital are some of the services that the Thalassemia and Sickle Cell Society (TSCS) in Hyderabad provides for Human Leukocyte Antigen (HLA)-matched blood-matter transplant-compatible patients. Their haploidentical Bone Marrow Transplantation (BMT) initiatives address donor shortages, particularly in communities with limited resources. Regional efforts to improve access to curative therapies are demonstrated by collaborations of a similar nature with the Sankalp Foundation's headquarters in Bangalore (Thalassemia and Sickle Cell Society 2025).

One of the main strategies employed by the healthcare system to lower the number of new thalassaemia patients is genetic counselling. For this reason, genetic counselling programs are quite successful in preventing illness. By having a better understanding of the disease's nature, effects, transmission, risks and prevention strategies, parents can make more informed decisions with the aid of genetic counselling regarding ways to prevent it, such as using family planning, receiving an antenatal diagnosis, having a therapeutic abortion, or any combination of these (Greco and Marino 2022).

Awareness Campaigns: Increasing public awareness about thalassaemia through educational programs can promote early screening and reduce the stigma associated with the disease.

- Policy development: Implementing policies that support subsidised genetic testing, particularly in high-prevalence areas, can enhance access to diagnostic services.
- Community engagement: Collaborating with local communities and cultural leaders to address the challenges of consanguineous marriages and promote genetic counselling.

Research and Innovation

- Genetic Research: Continued research into the genetic basis of thalassaemia in South India can uncover new mutations and inform the development of novel diagnostic and therapeutic approaches.
- Technological Advancements: Investing in affordable and accessible genetic testing technologies can revolutionise thalassaemia screening and management.

Finally, these results add to earlier research that showed how common haemoglobinopathies are in India, especially β-thalassaemia, which has a big impact on tribal people (Ganesh et al. 2024). Consistently, recent data indicate that this disorder is one of the most common genetic disorders among the people of South Asia, as corroborated by various studies in India, Bangladesh and Pakistan. Recent genetic studies have shown that the high number of marriages between related family members, especially in rural and tribal areas, is a major factor in the spread of â-thalassaemia carrier traits.

This review also delves into the geographic distribution of specific mutations, including the IVS I-5 (G>C) and codon 15 (G>A), which have consistently been reported as the most prevalent mutations in South India (Panigrahi and Marwaha 2007). Such findings are in sync with the regional

mutation profiles documented in Karnataka and Andhra Pradesh, where similar mutations are cited. In conclusion, a full population screening in Tamil Nadu found that between 1 percent and 3 percent of people there are carriers of â-thalassaemia. This supports the idea of putting in place targeted genetic screening programs in that area (Noor et al. 2020).

The economic burden of thalassaemia is immense, with related estimates stating that to the tune of INR 1.5 million are treated for a year on a single child with β-thalassaemia major (Nhac-Vu et al. 2023). This imposes considerable parental involvement in the treatment, especially in a socioeconomically challenged setting without state support for genetic counselling and widespread prenatal diagnostics (Clarke and Wallgren-Pettersson 2019). The findings corroborate the literature, which discusses the difficulty of providing accessible care to thalassaemic patients, especially among severe resource limitations.

Gene therapies and molecular diagnostics have demonstrated some promising results, but their affordability and globalisation are still profound. Despite the success of gene therapy in a few countries, it still poses a significant financial burden for developing countries such as India and remains out of reach for the majority of patients (Cornetta et al. 2022). Next-generation sequencing (NGS) and high-throughput screening have opened an optimistic perspective of more precise and economic diagnosis. Yet again, this technique could be only implemented in a handful of central parts of India because of financial support and infrastructural constraints (John et al. 2021).

Finally, in tandem with ongoing research aimed at enhancing the accessibility, availability and affordability of genetic counselling and prenatal diagnostics in high-prevalence areas such as south India, which have a genetic predisposition to thalassaemia, there is a pressing need for the uniform implementation of effective public health policies.

CONCLUSION

Thalassaemia remains a significant genetic disorder in South India, with a complex spectrum of mutations that pose diagnostic and management challenges. By enhancing the understanding of the genetic basis of thalassaemia, one can improve screening, diagnosis and treatment strategies, ultimately reducing the burden of this disorder. Future research should focus on expanding genetic studies to uncover rare mutations, developing cost-effective screening methods, and exploring new therapeutic approaches such as gene therapy.

RECOMMENDATIONS

The action of combining carrier screening programs for thalassaemia should be medically eulogised in carriers and at-risk populations, particularly in regions with high consanguinity. This is to help early identification of carriers, hence curtailing incidences of Â-thalassaemia major from prompted reproductive choices. Moreover, there is an urgent call for improved affordable access to genetic counselling opportunities in rural and tribal communities. This is crucial in ensuring at-risk families are properly advised. In this respect, not only should community awareness be initiated through specific education campaigns promoting knowledge of disease risks for haemoglobinopathies, but also the actual context of these programs should be integrated into public health. Lastly, states should ensure that grants subsidise diagnostic interventions, thereby enhancing the recognition of other spectrum ranges, such as next-generation sequencing, and providing not only orientation, and awareness but also promising relief.

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CONFLICT OF INTERESTS

The authors do not declare any conflict of interest.

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