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Editorial

Understanding genomics in thalassemia: Spotlight on the α-Globin gene

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India has made significant progress in diagnosis and prevention of thalassemia. This was possible due to effective community outreach programs and public awareness about screening initiatives. The government's emphasis on thalassemia control has further contributed to accumulating valuable data on hemoglobinopathies. Given the country's vast diversity, the prevalence of various hemoglobinopathies varies across different regions. This diversity has also led to an increase in the diagnosis of compound heterozygous states, whose genotypes and phenotypes continue to challenge our understanding.[1]

Notably, most advancements in hemoglobinopathies and thalassemia research have focused on the β-variant. This focus is likely due to its higher prevalence, more severe clinical manifestations, and the availability of relatively cost-effective diagnostic tools such as hemoglobin (Hb) high-performance liquid chromatography (HPLC) and capillary zone electrophoresis (CZE). These tools facilitate the detection of carrier states and provide genetic counseling for at-risk couples. β-globin mutations, primarily point mutations, can be confirmed at the molecular level through Sanger sequencing, a technique that is both technically straightforward and affordable. As a result, prenatal genetic diagnosis for β-thalassemia has become increasingly accessible across the country.[2]

Diagnosing α-thalassemia is notably complex and presents unique challenges. Each chromosome 16 contains two α-globin genes, giving an individual a total of four α-globin genes. Molecular alterations in these genes include deletions and less commonly point mutations. Deletion of one or two α-globin genes is usually clinically silent and may go unnoticed in laboratory evaluations. The only subtle indicators might be slightly reduced mean corpuscular volume and mean corpuscular Hb in the absence of iron deficiency. In addition, a two-gene deletion may result in mildly reduced HbA_2 levels. Four α-globin gene deletions result in hydrops fetalis and are fatal *in utero*. Symptomatic forms of α-thalassemia, such as HbH disease or HbH-like syndromes involving three α-globin gene, typically manifest more prominently. These conditions can be classified as either deletional (three α-globin gene deletions causing HbH disease) or non-deletional (homozygous PolyA mutations, homozygous point mutations in the α-globin genes, or two-gene deletions coupled with a heterozygous point mutation). In such cases, Hb variant analysis typically reveals low HbA_2 levels along with a fast migrating, sometimes bifid, peak at 0.15–1 min retention time.[3,4] Non-deletional variants may also produce abnormal peaks at varying retention times, depending on the specific mutation. In the Indian population, some notable examples of non-deletional α-thalassemia variants include HbJ Meerut, Hb Koya Dora, and Hb Evanston.[5-7]

Molecular diagnosis of α-thalassemia typically requires both Sanger sequencing to identify point mutations and multiplex ligation-dependent probe amplification (MLPA) to detect deletions.

Next-generation sequencing (NGS) is now increasingly used for molecular diagnosis of thalassemia; however, α-globin genes are not well covered in the NGS platform due to very high homology between them. This limitation can occasionally result in false-positive or false-negative findings. Therefore, it is advisable to continue using conventional molecular diagnostic methods for α-thalassemia until NGS methodologies are further refined.[6] α-globin mutations are generally inherited from carrier parents; however, the occurrence of *de novo* mutations has been reported, adding complexity to the genetic landscape.[7]

Clinically significant phenotypes can also arise when α-globin gene multiplication coexists with a β-thalassemia trait. This combination can lead to a thalassemia intermedia phenotype, characterized by increased HbF and elevated HbA_2 levels on Hb HPLC or CZE.[8] Comprehensive molecular confirmation of such cases requires β-globin gene sequencing alongside α-globin gene MLPA.

Advances in genomics are paving the way for exciting developments in thalassemia diagnostics. It will be interesting to see how this influences the landscape of family counseling and pre-natal genetic diagnosis in future.

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