

Case Report

Alpha Thalassemia Allele Premarital Counseling (Hba2:C.*94a>G).

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Abstract

The polyadenylation (PA) signal of HBA2 (α PA:A→G) has a 30-UTR (3 primary untranslated region) single-nucleotide substitution due to the mutation HBA2:c.*94A>G (AATAAA>AATAAG; rs63751269). In the Arabian Peninsula, this pathogenic variant (CADD score: 14.92) occurs occasionally. It leads to transcription termination, ineffective mRNA processing, and maybe the use of a different, cryptic downstream polyadenylation signal. Because of this, premarital counseling regarding the fetal risk of hemoglobin H illness is complicated by the allele α T (or α T-Saudi). The moderate-to-severe microcytosis (mean red cell volume, MCV, 55 to 65 fL) caused by homozygous HBA2:c.*94A>G (α Ta/ α Ta) indicates significantly reduced hemoglobin synthesis (hemoglobin H illness). NM_000517.4:c.[2_-3delAC; - α 3.7] is a 3804-nucleotide deletion allele that causes mild microcytosis (MCV, 70 to 75 fL, alpha-thalassemia phenotype) when homozygous rightward - α 3.7. HBA2:c.*94A>G is therefore more harmful than - α 3.7. In compound heterozygosity, HBA2:c.*94A>G and - α 3.7, the MCV value is consistently 65 to 70 fL. A healthy couple that sought premarital counseling over their hemoglobinopathy is the subject of this study. The lady is compound heterozygous (- α 3.7/ α Ta, also known as -3.7/ α Ta), while the guy is homozygous for HBA2:c.*94A>G (α Ta/ α Ta). Their children would therefore have either the mother's (- α 3.7/ α Ta) or father's (α Ta/ α Ta) genotype. The parents' benign characteristics served as the primary foundation for the counseling. They married since neither of them had any symptoms and their anemia was clinically negligible.

Keywords : Arabian Peninsula; HBA2; HBA1; hemoglobin H disease.

INTRODUCTION

One or more of the HBA2 (hemoglobin-alpha locus 2, MIM#141850) or HBA1 (hemoglobin-alpha locus 1, MIM#141800) genes are faulty in alpha thalassemia (MIM#604131), an inherited blood disorder. Two copies of HBA2 and two copies of HBA1 (one copy on each of the two homologous chromosomes 16) make up the typical genotype. Although HBA2 and HBA1 have the identical coding sequence, their introns and the 5' and 3' UTRs are different, which influences how the gene is expressed [1]. For instance, compared to HBA1, HBA2 encodes 2-3 times as much protein. Alpha thalassemia comes in four different types. (1) A somewhat low MCV (75 fL to 80 fL) is caused by the silent carrier (three functioning genes). (2) The two functioning genes that cause alpha thalassemia, which results in a more noticeable microcytosis (MCV, 70 $\pm$ 5 fL). Cis deletion (α or null allele) is the term used to describe the deletion (or inactivation) of both HBA2 and HBA1 on a single chromosome. This variant, which is common in Southeast Asia and the Mediterranean region, increases the risk of severe alpha-thalassemia in the fetus. Trans deletion (α +) is the term used to describe the

deletion of HBA2 or HBA1 on a single chromosome. Two varieties of deletional alpha-thalassemia exist. The Arabian Peninsula, Africa, and the Mediterranean region are home to the 3.7 kb deletion (rightward type; - α 3.7; HBVAR#1076), as seen in Figure 1B. The 4.2 kb deletion (leftward type, - α 4.2) is present throughout the Pacific Islands and Southeast Asia. (3) Hemoglobin H illness (children of a parent with α thalassemia phenotype and another with silent carrier, for example, one functioning gene). Crucially, the hemoglobin H (not to be confused with "hemoglobin H disease") unpaired β -chain aggregates are more soluble than the unpaired α -chain aggregates that are present in β -thalassemia. As a result, mild anemia rather than severe anemia is present in people with hemoglobin H illness. (4) Four faulty genes, such as those found in children of parents with the α thalassemia trait, cause hemoglobin Bart's hydrops fetalis syndrome, which is incompatible with life [2]. Figure 1. (A) Between 172876 and 173710, the human HBA2 gene was found on chromosome 16 (NCBI RefSeq Accession: NC_000016.10). Green blocks represent the three HBA2 exons. Exon 1's light green indicates 5' UTR, while exon 3's light green indicates 3' UTR. The range of 173689 to 173694 is where the

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polyadenylation signal (AATAAA) is found. AATAAG is the new sequence in the α T variation (HBA2:c.*94A>G; rs63751269). (B) The human chromosome 16 (NCBI RefSeq Accession: NC_000016.10) contains the HBA2 and HBA1 genes, which are situated between 172876 and 173710 and 176680 and 177522, respectively. The three HBA1 exons are displayed as yellow blocks, and the three HBA2 exons are displayed as orange blocks. As seen, 3.7 kilobases are deleted in the $-\alpha$ 3.7 versions. In the United Arab Emirates, α + thalassemia trait is highly prevalent. HBA2 or HBA1 abnormalities were present in 49% of the infants in one investigation; most of them had a $-\alpha$ 3.7 [3]. The prevalence of the α + thalassemia trait varied between 15% and 20% in different investigations [4,5]. Accordingly, the non-deletional variant HBA2:c.*94A>G is less common in the area, whereas $-\alpha$ 3.7 is the most prevalent mutation [6–8].

Three normal types are formed by the four hemoglobin chains (α , β , γ , and δ): A2 (2 α with 2 δ , 1.5% to 3.5%), F (2 α with 2 γ , 21.5% to 3.5%), and A2 (2 α with 2 β , 93% to 97%). A2 is normal in the alpha-thalassemia trait, whereas the latter two hemoglobins' percentages rise in the beta-thalassemia phenotype because they lack β chains. Therefore, determining A2 accurately is essential.

CASE

Premarital counseling for hemoglobinopathy was provided to a healthy couple. Table 1 displays the findings of their inquiry. They had no symptoms, and premarital screening was the only time they discovered they had anemia. MCV <65 fL indicated moderate-to-severe microcytosis in both of them. The woman's hemoglobin analysis, serum ferritin, and moderate anemia were all normal. Multiplex PCR analysis, or MLPA, revealed heterozygous $-\alpha$ 3.7. According to HBA2 and HBA1 sequencing studies, heterozygous HBA2:c.*94A>G was found. According to Table 1 and Figure 1C, her genotype was compound heterozygosity ($-\alpha$ 3.7/ α Ta), the less common non-deletional variant [NM_000517.6(HBA2):c.*94A>G; rs63751269], and the common deletional variant (NM_000517.4:c.[-2_-3delAC; $-\alpha$ 3.7], CA16602246, Variation ID: 38636, VCV000038636.3).

DISCUSSION

For almost all eukaryotic messenger RNAs (mRNA), polyadenylation, or the addition of a poly(A)-tail, is a necessary post-transcriptional alteration [9–11]. For mRNA to remain stable in the cytoplasm, this step is essential. The polyadenylation site, or highly conserved sequence motif AATAAA, guarantees effective cleavage of the main transcript in humans and the subsequent addition of the poly(A)-tail [12]. Rarely do variations in this signal sequence occur, and

they are usually linked to other diseases or the utilization of different polyadenylation sites [13]. The third exon of HBA2, which is located 89 bases downstream of the translation stop codon, encodes the typical signal sequence (Figure 1). The translated mRNA changes from AAUAAA to AAUAAG due to the mutation HBA2:c.*94A>G, which causes ineffective mRNA processing. As a result, this difference significantly affects the amounts of the translated gene product, hemoglobin α protein, and mature mRNA generated by HBA2. Notably, HBA2 encodes 2–3 times as much protein as HBA1 [14], which accounts for HBA2's stronger effect on alpha-thalassemia.

To determine the fetal risk of "hemoglobin H disease" or "hemoglobin Bart's hydrops fetalis syndrome" in the pair under study, phenotypic and genetic research were required. According to the findings, the offspring's anticipated genotypes were either (α Ta/ α Ta) for the mother or ($-\alpha$ 3.7/ α Ta) for the father. They married since they were both in good health and their anemia was not clinically noticeable. Other family members can potentially benefit from the identified genes [15–17].

CONCLUSIONS

People with homozygous HBA2:c.*94A>G (α Ta/ α Ta) exhibit low hemoglobin A2, high hemoglobin H, moderate anemia (hemoglobin, 20–30 g/L below normal), and moderate-to-severe microcytosis (MCV, 55–65 fL). People with $-\alpha$ 3.7/ α Ta have normal hemoglobin analysis, mild anemia (hemoglobin 10–20 g/L below normal), and moderate microcytosis (MCV, 60–65 fL). Therefore, the " $-\alpha$ 3.7 deletion" is less harmful than the HBA2:c.*94A>G allele. It reduces HBA2 expression by 75% [10]. Additionally, the fact that MCV is significantly lower in $-\alpha$ 3.7/ α Ta than in homozygous α + thalassemia ($-\alpha$ 3.7/ $-\alpha$ 3.7) implies that HBA2:c.*94A>G may have an impact on HBA1 expression. When moderate-to-severe microcytosis is present, prenatal counseling on alpha-thalassemia requires studies (MLPA and sequencing analysis) of HBA2 and HBA1.

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