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Letter to the Editor: Open Access

Diverse Genotype Presentation of the Saudi-Type Poly A Signal Mutation (αTsaudiα) in the Population of Bahrain

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α—Thalassemia is quite prevalent in the population of Bahrain reaching a frequency of 24.3% based on neonates screening of Hb Bart's in cord blood hemolysates [1]. In a preliminary report we found five different α-thalassemia determinants as the underlying molecular defects for α-thalassemia in our population [2]. The first most common α-thal determinant uncovered in that report was the Saudi-type polyadenylation signal mutation that is found in α2-globin gene ($\alpha^{TSaudi}\alpha$) [AATAAA$^{\diamond}$AATAAG; c.*94A>G] [2,3,4]. In this letter we presented the diverse genotype combinations of the ($\alpha^{TSaudi}\alpha$) haplotype in our population and their relevant phenotypes.

A total of 1187 patients with α-thalassemia phenotype presentation have been recruited for this investigation. Preliminary diagnosis of α-thalassemia was based on low hematological indices (MCV and MCH) of the red blood cells and/or persistently low hemoglobin levels, along with low or normal levels of HbA2 and absence of iron deficiency [5,6]. The molecular diagnosis of α-thalassemia was established by using a commercially available α-thalassemia strip assay (α-Globin StripAssay, ViennaLab Diagnostics GmbH) and direct nucleotide sequencing for further confirmation.

The spectrum of phenotype presentations for the ($\alpha^{TSaudi}\alpha$) genotype combinations ranges between hemoglobin H (Hb H) disease and α-thalassemia trait phenotype with variable severity.

The first molecular defect causing HbH disease in our population is homozygosity for the ($\alpha^{TSaudi}\alpha$) haplotype, i.e., the ($\alpha^{TSaudi}\alpha/\alpha^{TSaudi}\alpha$) genotype, which is by far the most common molecular basis of Hb H disease in this population. A total of 49 patients were uncovered with this genotype and a representative 15 patients are introduced in Table 1. These patients are presented with moderate to severe level of anemia (Hb ranges: 7.4-9.7g/dL). They persistently show Hb H peak fraction on HPLC of their RBC hemolysates with HbH level ranges from 7.5 to 27.2 % of total hemoglobin. In addition, most of these patients are presented with elevated level of reticulocytes (>3.0%), an indication of hematopoitic stress due to persistent anemia. Moreover, significant number of these patients is undergoing infrequent blood transfusion which is in line with variable phenotype presentation of Hb H disease in other populations [7-9]. Although this genotype is inactivating only two α-globin genes it gives rise to a severe form of Hb H disease whereas the inactivation of three α-globin genes is commonly encountered in Hb H disease [10]. This unusual effect of the ($\alpha^{TSaudi}\alpha$) mutation is largely attributed to a down regulation effect of this mutation on the linked α1-globin gene as a result of transcriptional interference as was suggested before [11,12].

Table 1: Hematological parameters in selected patients harboring the ($\alpha^{TSaudi}(\alpha/(\alpha^{TSaudi}(\alpha)$ genotype

No.	Gender/Age	Hb (g/dL)	RBC (x10^{12}/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	HbA2 (%)
1	F/34	7.4	3.9	61.7	18.7	30.2	1.5
2	M/69	7.4	4.0	64.5	18.4	28.6	1.6
3	F/18	8.5	4.7	59.2	17.9	30.1	1.3
4	F/35	8.2	4.5	62.4	18.2	29.2	1.6
5	F/29	9.5	5.3	60.0	17.9	29.8	1.7
6	F/45	7.8	4.3	59.1	17.9	30.3	1.5
7	F/32	9	4.7	59.5	18.8	31.6	2.2
8	F/51	8.1	4.6	62.0	17.4	28.0	1.5
9	F/47	9.2	5.1	51.0	18.0	35.0	1.9
10	F/31	7.8	4.5	60.8	17.3	28.5	2.2
11	F/35	8.2	4.6	59.3	17.7	29.8	1.7
12	M/35	9.6	5.1	59.2	18.7	31.5	1.8
13	M/13	9.3	5.0	56.1	18.3	32.6	2.1
14	M/11	7.8	4.4	64.0	18.0	28.0	1.9
15	M/39	8.9	4.9	62.1	18.3	29.4	1.5

*ND: Not Determined

The second genotype underlying Hb H disease in this population is compound heterozygosity of the ($\alpha^{TSaudi}\alpha$) haplotype *in trans* with the IVS I donor-site pentanucleotide deletion mutant in α2-globin gene on the other chromosome [($\alpha^{Hph}\alpha/$); c.95+2_95+6del TGAGG] [13]. This genotype combination [i.e., ($\alpha^{TSaudi}\alpha/\alpha^{Hph}\alpha$)] was discovered in a total of 25 patients and all are presented with relatively mild-to-moderate form of Hb H disease with total Hb levels ranging from

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Table 2: Hematological parameters in selected patients harboring the (α^{TSaudi}(α/(α^{Hph}(α) genotype

No.	Gender/Age	Hb (g/dL)	RBC (x10^{12}/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	HbA2 (%)
1	M/45	10.9	6.1	57.7	17.8	30.8	2.3
2	F/35	9.9	5.5	58.2	18.0	30.9	2.5
3	F/30	9.2	4.8	59.4	18.8	31.6	2.4
4	F/49	10.3	5.3	58.0	19.2	33.1	2.1
5	F/10	9.2	5.0	58.3	18.3	31.4	2.5
6	F/14	9.9	5.4	60.0	19.0	31.0	2.1
7	M/9	9.9	5.5	61.0	18.0	30.0	2.2
8	M/9	9.0	5.4	55.7	16.8	30.1	2.1
9	F/43	9.4	4.8	61.9	19.5	31.5	2.2
10	F/70	9.8	5.2	59.6	18.7	31.4	2.5
11	M/7	9.0	4.9	57.8	18.4	31.9	2.6
12	F/19	9.4	5.7	54.0	17.0	31.0	2.0
13	F/21	10.1	5.2	61.2	19.4	31.7	2.2
14	F/23	10.8	5.7	60.0	19.1	31.9	2.1
15	M/61	11.3	6.0	60.0	18.0	30.0	2.3

*ND: Not Determined

Table 3: Average hematological values for patients harboring various combinations of the (α^{TSaudi}α) genotype along with values for wild type genotype (αα/αα) in the population of Bahrain

Genotype	n	Male/Female	Hb (g/dL)	RBC (x10^{12}/L)	MCV (fL)	MCH (pg)	MCHC (g/dL)	HbA2 (%)
(αα/αα)	38	13/25	12.7* (1.4)	4.4 (0.6)	85.1 (4.6)	28.7 (2.0)	33.7 (1.3)	2.9 (0.2)
(α^{TSaudi}α/αα)	28	17/11	12.0 (1.2)	5.0 (0.4)	74.3 (3.4)	24.1 (1.1)	32.4 (1.1)	2.5 (0.5)
$_{(-\alpha}$3.7$_{/\alpha}$**TSaudi**$_{\alpha)}$	52	24/28	10.8 (1.0)	5.3 (0.6)	64.1 (2.6)	20.2 (0.9)	31.6 (1.0)	2.6 (0.2)
$_{(-\alpha}$4.2$_{/\alpha}$**TSaudi**$_{\alpha)}$	12	4/8	10.6 (2.0)	5.2 (1.1)	63.2 (3.9)	20.1 (1.2)	31.8 (0.9)	2.6 (0.3)

*Values are means (±SD)

9.0g/dL to 11.3g/dL (Table 2). None of these patients require blood transfusion.

Comparison of hematological parameters between the (α^{TSaudi}α/α^{TSaudi}α) genotype and the (α^{TSaudi}α/α^{Hph}α) genotype by using the Student's T-test revealed highly significant difference (P<0.001) in Hb levels (8.5 ± 0.7 vs. 10 ± 0.8), RBC counts (4.6 ± 0.4 vs. 5.4 ± 0.5) and HbA2 levels (1.7 ± 0.3 vs. 2.3 ± 0.2) [values are means ± SD for (α^{TSaudi}(α^{TSaudi}(α vs. (α^{TSaudi}(α^{Hph}(α, respectively]. In contrast no difference was observed between these two genotypes in MCV (60 ± 3.5 vs. 58.7 ± 2.6) and MCH (18.1 ± 0.5 vs. 18.3 ± 0.9) (P>0.05) [n=33 for(α^{TSaudi}(α^{TSaudi}(α and n=25 for (α^{TSaudi}(α^{Hph}(α]. In summary, these two genotypes are presented with the most severe phenotype of Hb H disease in this population.

Other genotype combination of the Saudi type poly A signal mutation that we uncovered includes the (-$\alpha^{3.7}$/ $\alpha^{T\ Saudi}$α) genotype that we found in 52 patients (Table 3). In addition, we found 12 patients with the (-$\alpha^{4.2}$/α^{TSaudi}α) genotype. Indeed, both of these genotypes are presented, as expected, with the same level of hematological severity and mild presentation of Hb H disease (Table 3). Finally we uncovered 40 patients with the (α^{TSaudi}α/αα) genotype . These simple heterozygotes are consistently presented with α-thalassemia trait phenotype (Table 3).

In summary, this report presents our findings in regard of the (α^{TSaudi}α) genotype combinations in the population of Bahrain and their phenotypes. Further investigations in various developmental stages are warranted to clearly understand the natural history of (α^{TSaudi}α) genotype combinations.

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