Interaction between (--^{SEA}) α-thalassemia deletion and uncommon non-deletional α-globin gene mutations in Chinese patients

We describe the interaction of (—^{SEA}) α-thalassemia deletion with poly-A signal mutation at the α2-globin gene in one Chinese family and with hemoglobin (Hb) Westmead [α_2 122 (H5) His→Gln] in another family, and show that the spectrum of non-deletional α-globin gene mutations encountered in our population is wider than previously reported.

There is evidence[1] that non-deletional forms of Hb H disease produce a more severe clinical picture than deletional forms. The non-deletional α-globin gene mutations hitherto recognized in Chinese patients include Hb Constant Spring, Hb Quong Sze, DGAG at codon 30 of α_2, GGC→GAC at codon 59 of α_2 and AGG→AAG at codon 31 of α_2. We describe one Chinese family in which the (—^{SEA}) α-thalassemia deletion occurs in association with AATAAA→AATGAA mutation at polyadenylation site of the α_2 -globin gene[2] and another family in which the deletion occurs in association with Hb Westmead [α_2 122 (H5) His→Gln][3] respectively (Table 1).

Family A. The daughter presented in infancy with pallor and had previously received several units of blood transfusion. Her height and weight were at the 90th and 75th percentiles of normal. She had hepatosplenomegaly (liver 4 cm and spleen 3 cm below costal margins). As her steady state Hb was 9.8 g/dL, she did not require regular transfusion. Her brother presented at the age of 5 with mild pallor and slight jaundice. While his steady state Hb was 8.3 g/dL and did not require regular blood transfusion, his Hb dropped to 5.4 g/dL as a result of a viral illness at the age of 11, for which 2 units of blood were transfused. His height and weight were both at the 50th percentile of normal. Like his sister, he also had hepatosplenomegaly (liver 3 cm and spleen 2 cm below costal margins). Both siblings were compound heterozygotes for AATAAA→AATGAA mutation at poly-A site of the α_2 and (—^{SEA}) α-thalassemia deletion (--^{SEA}/$\alpha^T\alpha$). The father was a carrier of (—^{SEA}) α-thalassemia deletion while the mother, a native of Guangdong province, was a silent carrier of the poly-A signal mutation.

Family B. As the mother was a known α-thalassemia carrier, the Hb pattern was investigated in her 2-day old daughter. The pattern showed 20% Hb Barts on electrophoresis. There was also red cell microcytosis despite a normal Hb level. The baby had normal growth and development. Hb pattern analysis at 10 months of age showed 0.5% of red cells harbored Hb H inclusion bodies, with no abnormality on chromatography (Bio-Rad Variant). She had no pallor or hepatosplenomegaly, and her body weight and height were at the 25th percentile of normal. Genotyping revealed compound heterozygosity for Hb Westmead and (—^{SEA}) α-thalassemia deletion (—^{SEA}/$\alpha^W\alpha$). Her mother was a carrier of (--^{SEA}) α-thalassemia deletion while her father, a native of Guangdong province, was a silent carrier of Hb Westmead.

The two siblings in family A represent the first reports of Hb H disease caused by coexistence of (--^{SEA}) α-thalassemia deletion and the AATAAA→AATGAA mutation at the poly-A signal of α_2. This point mutation at the poly-A site leads to an elongated and non-functional transcript and, due to transcriptional interference,[4] the downstream α_1 is unable to increase its expression.[5] Therefore, a more severe Hb H disease phenotype may result, and indeed this is supported by the young age of onset, hepatosplenomegaly and history of blood transfusion in our two patients. Hb Westmead, seen in family B, is prevalent in the Guangxi province of China,[6] is mildly unstable,[7] and cannot be detected by routine chromatography.[8] The diagnosis is made incidentally from hematologic investigations. The daughter in family B shows no symptoms. A case could be made for screening non-deletional α -globin gene mutations by molecular techniques in partners of known carriers of (—^{SEA}) α-thalassemia deletion. This would facilitate the provision of genetic counseling and prenatal diagnosis to at risk couples for more severe forms of Hb H disease.[9] The acceptability of such an approach should be investigated in couples with children affected by Hb H disease.

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Key words: Hb H disease, (--^{SEA}) α-thalassemia deletion, poly-A signal mutation, Hb Westmead, Chinese.

Table 1. Clinical and hematologic findings of the subjects described in this report.

Subject	Age (yrs)	Hb (g/dL)	MCV (fL)	MCH (pg)	Retics (%)	HbA2 (%)	HbH Bodies (%)	Transfusion history	α-genotype
Family #1									
Father	56	15.8	75.6	23.4	< 2	2.1	occ	Nil	--^{SEA}/αα
Mother	44	13.1	87.8	27.5	< 2	2.8	neg	Nil	αα/$\alpha^T\alpha$
Daughter	15	9.8	69.3	21.1	5.2	1.2	95	several units	--^{SEA}/$\alpha^T\alpha$
Son	12	8.3	64.0	19.0	2.4	1.9	65	2 units	--^{SEA}/$\alpha^T\alpha$
Family #2									
Father	20	15.1	91.6	29.9	< 2	2.8	neg	Nil	αα/$\alpha^W\alpha$
Mother	19	11.7	67.2	21.7	< 2	2.6	occ	Nil	--^{SEA}/αα
Daughter	1	11.4	58.3	20.0	3.7	2.6	0.5	Nil	--^{SEA}/$\alpha^W\alpha$

Key: Hb; hemoglobin; MCV, mean corpuscular volume; MCH, mean cell Hb; Retics, reticulocytes; occ, occasional; neg, negative; α^T, AATAAA→AATGAA mutation at polyadenylation site of the α2-globin gene; α^W, Hb Westmead [α_2 122 (H5) His→Gln]. Reference range: Hb, 13.0-18.0 g/dL (male), 11.5-16.5 g/dL (female); MCV, 80-97 fL; MCH, 27-32 pg; Retics, < 2%; HbA_2, 2.3-3.0%.

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