The Cretan type of nondeletional hereditary persistence of fetal hemoglobin in an Iranian family.

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LETTER TO THE EDITOR

The Cretan type of nondeletional hereditary persistence of fetal hemoglobin in an Iranian family

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Dear Editor,

The increase of fetal hemoglobin (HbF), in adult life, is mainly due to large deletions within β-globin cluster in hereditary persistence of fetal hemoglobin (HPFH) and δβ-thalassemia or in some cases of nondeletional HPFH (nd-HPFH) by mutations in promoter region of γ-globin genes [1–3]. Several nd-HPFH mutations have been reported; most of these mutations occur in transcription factor binding sites, creating new factor binding motifs or disrupting the existing ones [2]. The Cretan type of nd-HPFH (Aγ-158 C>T) is characterized by slightly elevated HbF levels (2.9–5.1%) and normal hematological indices [4]. This mutation has resulted from two independent gene conversion events [4, 5]. It is identical to Gγ-globin gene *Xmn*I polymorphism (Gγ-158 C>T) which also occurs in healthy individuals.

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In this study, we report the Cretan type of nd-HPFH for the first time in Iranian families. The family was from Khozestan, south of Iran with Arabic ethnic origin. They were distinguished by slight elevation of HbF levels and normal hematological indices (Table 1).

After obtaining written informed consent, genomic DNA was extracted from peripheral blood leukocytes using salting out method [6]. The 5′ regulatory regions of the Aγ- and Gγ-globin genes were analyzed by DNA sequencing in three related cases named F.A, K.A, M.A (Fig. 1).

The genotype of α- and β-thalassemia alleles in studied individuals had been identified previously. It is worth mentioning that no mutation was detected in the β-globin genes for these cases.

All three cases showed the presence of the Aγ-158 C>T as a rare mutation (Fig. 1), Aγ-588 G >A and Gγ-158 C>T polymorphisms. Aγ-158 C>T mutation is identical to Gγ-globin gene *Xmn*I polymorphism and creates an additional *Xmn*I restriction site.

As we have shown in Table 1, F.A, K.A, and M.A cases had C/T, T/T, and C/T genotypes for Aγ-158 C>T locus, respectively. The corresponding HbF levels for these genotypes were 4%, 0.2%, and 2.7%. Although F.A and M.A cases had raised HbF levels correlating with their C/T genotypes, K.A with 0.2% HbF and T/T genotype was unexpected, considering previous studies proposing functional role for T allele of Aγ-158 promoter [4, 5].

These findings show that the increased HbF level is not completely under the influences of T allele. Therefore, our observation from these three related cases showed that probably in addition to Aγ-158 C>T mutation other factors play a role in expression of Aγ-globin gene.

Table 1 Hematological indices of the three adult cases with the Cretan type of nondeletional hereditary persistence of fetal hemoglobin

Hematological index	Offspring F.A	Mother K.A	Offspring M.A
Hb (g/dl)	12.2	14.1	?
Hct (%)	35.7	41.5	?
RBC (106)	4.08	4.7	?
MCH (pg)	30.1	30.1	27.8
MCV (fl)	87.5	88.5	82.6
HbA (%)	92.8	96.5	95.3
Hb A2 (%)	3.2	3.3	2
HbF (%)	4	0.2	2.7
Gγ-*Xmn*I	−/+	+/+	+/+
Aγ-158 C>T	C/T	T/T	C/T
Sex/age (years)	F/18	F/45	F/22

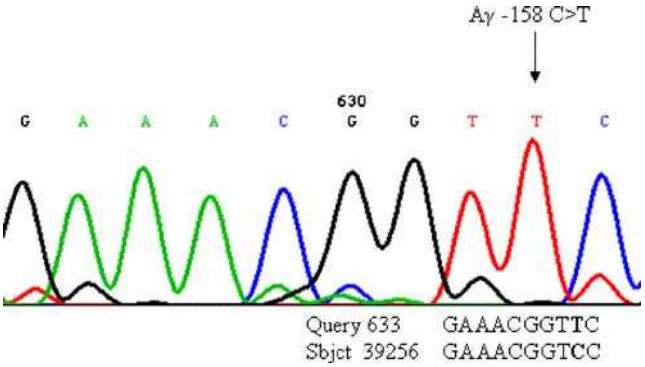

Fig. 1 Sequence analysis showing Aγ-158 C>T mutation of the Aγ-globin gene

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