Abnormal Hemoglobins in Turkey

Çiğdem ALTAY

Department of Pediatrics, Pediatric Hematology Unit, Faculty of Medicine, University of Hacettepe, Ankara, TURKEY

ABSTRACT

The presence of HbS was reported in Turkey for the first time in the late fifties by Aksoy et al. This was followed by other reports by the same author revealing the presence of several other abnormal hemoglobins in Turkey. So far up to present 42 abnormal hemoglobins have been identified in the Turkish population. In addition to the studies conducted in Turkey, many European researchers reported their findings in the immigrant Turkish population in their countries. This review tries to cover the tremendous efforts in this field.

Key Words: Abnormal hemoglobin, Turkey.

In the late fifties the presence of HbS [beta6

Table 1. Abnormal hemoglobin variants reported from Turkish subjects

Name	Structure	Ref numbers
a. Variants of the alpha-chain (single base changes)		
1. O-Padova	a30 (B11) Glu->Lys (GAG->AAG)	37
2. Hasharon	a47 (CE5) Asp->His (GAC->CAC)	34
3. Montgomery	a48 (CE6) Leu->Arg (CTG->CGG)	34
4. Adana	a59 (E8) Gly->Asp (GGC->GAC)	42,49
5. J-Anatolia	a61 (E10) Lys->Thr (AAG->ACG)	48
6. Ube-2	a68 (E17) Asn->Asp (AAC->GAC)	49
7. Q-İran	a75 (EF4) Asp->His (GAC->CAC)	16
8. Moabit	a86 (F7) Leu->Arg (CTG->CGG)	46
9. M-Iwate	a87 (F8) His->Tyr (CAC->TAC)	50
10. Çapa	a94 (G1) Asp->Gly (GAC->GGC)	51
11. G-Georgia	a95 (G2) Pro->Leu (CCG->CTG)	52
12. Strumica	a112 (G19) His->Arg (CAC->CGC)	53
13. J-Meerut (J Birming ham)	a120 (H3) Ala->Glu (GCG->GAG)	54
b. Variants of the beta-chain (single base changes)		
14. S	ß6 (A3) Glu->Val (GAG->GTG)	1,2
15. C	ß6 (A3) Glu->Lys (GAG->AAG)	55
16. Ankara	ß10 (A7) Ala->Asp (GCC->GAC)	57
17. E-Saskatoon	ß22 (B4) Glu->Lys (GAA->AAA)	14,58
18. G-Coushatta	ß22 (B4) Glu->Ala (GAA->GCA)	59,60
19. D-İran	ß22 (B4) Glu->Gln (GAA->CAA)	34
20. E	ß26 (B8) Glu->Lys (GAG->AAG)	3,7,22,23,24
21. Knossos	ß27 (B9) Ala->Ser (GCC->TCC)	15,61
22. Hakkari	ß31 (B13) Leu->Arg (CTG->CGG)	43
23. G-Copenhagen	ß47 (CD6) Asp->Asn (GAT->AAT)	34
24. Summer Hill	ß52 (D3) Asp->His (GAT->CAT)	36
25. Hamadan	ß56 (D7) Gly->Arg (GGC->CGC)	12
26. J-Antakya	ß65 (E9) Lys->Met (AAG->ATG)	38
27. City of Hope	ß69 (E13) Gly->Ser (GGT->AGT)	15
28. J-İran	ß77 (EF1) His->Asp (CAC->GAC)	62
29. G-Szuhu	ß80 (EF4) Asn->Lys (AAC->AAA or AAG)	63
30. İstanbul Saint Etienne	ß92 (F8) His->Gln (CAC->CAA or CAG)	35,64
31. N-Baltimore	ß95 (FG2) Lys->Glu (AAG->GAG)	41
32. Köln	ß98 (FG5) Val->Met (GTG->ATG)	34,44
33. Los Angeles (D-Punjab)	ß121 (GH4) Glu->Gln (GAA->CAA)	19,65-67
34. O-Arab	ß121 (GH4) Glu->Lys (GAA->AAA)	9,10,29,34,68,69
35. Beograd	ß121 (GH4) Glu->Val (GAA->GTA)	13

Table 1. Abnormal hemoglobin variants reported from Turkish subjects (continuation)

Name	Structure	Ref numbers
36. Sarrebourg	ß131 (H9) Gln->Arg (CAG->CGG)	70
37. Brockton	ß138 (H16) Ala->Pro (GCT->CCT)	71
c. Variants of the agamma chain (single base changes)		
38. F-Başkent	128 (H6) Ala->Thr (GCT->ACT)	72
d. Hybrid HBS		
39. Lepore-Boston-Washington		34, 73,74
40. P-Nilotic		75
e. Hemoglobins with elongated alpha chains		
41. Constant Spring (or CS)	alpha142 (H19) (plus 31 residues)	34
f. Hemoglobins with longer or shorter beta chains due to deletions and insertions of certain aminoacid residus		
42. Antalya Unstable		45

Studies of patients: Routine hemoglobin electrophoresis in patients with chronic and mild to severe hemolytic anemia has helped identification of several abnormal hemoglobins in homozygous or compound heterozygous states or unstable hemoglobins as dominant form.

So far up to present 42 abnormal hemoglobins have been identified in the Turkish population. Thirteen of the 42 abnormal hemoglobins were alpha chain variants, 24 beta chain, one gamma chain, the two hybrid hemoglobins and two structural changes: elongated a chain and one deletion/insertion of ß chain (Table 1a-f, Table 2). Some of these abnormal hemoglobins were originally described in the Turkish population by laboratories in Turkey or in Europe or as a result of collaborative efforts[12-14,16,19-75] (Table 1a-f).

Unstable hemoglobins: Eight of the 42 abnormal hemoglobins were unstable (Table 3). Hb İstanbul ß92 (F8) (His->Gln), (CAC->CAA or CAG) is an unstable hemoglobin variant first reported from a young Turkish patient by Aksoy[35]. Coincidentally, the same variant was reported by French researchers as Hb Saint Etienne in another patient[64]. Quantity of abnormal hemoglobin in heterozygotes is around 25% high level (20%)

Table 2. Distribution and characteristics of abnormal hemoglobins according to the affected chain

	Abnormal chain				
Characteristic	Alpha	Beta	Gamma	Hybrid	Total
Stable	9	19	1	2	31
Unstable	4	2	-	-	6
Thalassemic	-	3	-	-	3
Elongated	1	-	-	-	1
Del/inv	-	1	-	-	1
Total	14	25	1	2	42

Table 3. Unstable hemoglobins

Name	Structure	
1. Hasharon	a47 (CE5) Asp->His	GAC->CAC
2. Adana	59 (E8) Gly->Asp	GGC->GAC
3. Moabit	86 (F7) Leu->Arg	CTG->CGG
4. Çapa	94 (G1) Asp->Gly	GAC->GGC
5. Hakkari	31 (B13) Leu->Arg	CTG->CGG
6. İstanbul (St Etienne)	92 (F8) His->Gln	CAC->CAA or CAG
7. Köln	98 (FG5) Val->Met	GTG->ATG
8. Constant Spring (or CS)	alpha142 (H19)	
9. Antalya	deletion in ß-chain	

of HbF present[47]. This abnormal hemoglobin had an electrophoretic mobility at pH 8.6. between HbF and HbS. Hb İstanbul and HbA separate at alkaline pH, Hb İstanbul moves between HbS and HbC[47]. Hb Hakkari, [ß31 (B13) Leu->Arg] and Hb Adana [a59 (E8) (Gly->Asp)] are two abnormal hemoglobins that are too unstable to detect by electrophoresis or by in vitro chain synthesis[42,43,76]. Large inclusions were present in erythroblasts in patients with Hb Hakkari [ß31 (B13) Leu->Arg] and HbF level was 33% of the total hemoglobin[43]. The patient was transfusion dependent even after splenectomy. The patients with Hb Adana [a59 (E8) (Gly->Asp)] had a°-thalassemia in trans. In these patients, Hb Barts, rather than HbH, is the second major hemoglobin after HbA[42,76]. In addition of these three hemoglobins there are two other unstable hemoglobins, namely Hb Moabit [a86 (F7) Leu->Arg] and Hb Köln [ß98 (Val->Met) (GTG->ATG)][34,44,46,50]. Hb Moabit [a86 (F7) Leu->Arg] was diagnosed in a Turkish patient in Switzerland[46]. Hb Köln [ß98 (Val->Met) (GTG->ATG)] is one of the most common abnormal hemoglobins reported from several countries (Table 1a,b, Table 3)[47]. Although this variant is highly unstable, it can be identified and measured by electrophoretic methods. Hb Köln [ß98 (Val->Met) (GTG->ATG)] was reported in three unrelated Turkish families (Table 1a-f, Table-3)[34,44,77]. It is important to note that these 3 highly unstable hemoglobins (Hb İstanbul, Hb Hakkari and Hb Köln) occurred as de novo mutations (Table 1a-f, Table 3).

It seems that in some of the highly unstable hemoglobins of ß-chain, such as Hb İstanbul and Hb Hakkari, elevation of HbF is common[35,43]. Therefore, in patients with severe anemia, the detection of increased HbF could be suggestive of the presence of an unstable hemoglobin of ß-chain variant after exclusion of ß-thalassemia.

Hb Antalya results from a small deletion and insertion of ß-gene (Table 1f)[45]. The patients have elevated HbA2 and microcytosis[45]. However, the clinical and hematological presentation is more severe than a simple heterozygous ß-thalassemia. Although no abnormal hemoglobin was observed in electrophoresis, DNA analysis revealed a small deletion and insertion which resulted in a mildly unstable variant and ß-thalassemia[45]. Therefore, this variant is included in the list of both unstable and thalassemic hemoglobins.

Thalassemic Abnormal Hemoglobins

The list of the thalassemic hemoglobins is given in the (Table 4). Among the three thalassemic abnormal hemoglobins Hb Knossos [beta27 (B9) (Ala->Ser)] is the one that can not be detected by simple electrophoretic examinations. Hb Knossos and HbA can be separated by IEF; Hb Knossos

Table 4. Thalassemic hemoglobinopathies

1. HbE	ß26 (B8) Glu->Lys	GAG->AAG
2. Hb Knossos	ß27 (B9) Ala->Ser	GCC->TCC
3. Hb City of Hope	ß69 (E13) Gly->Ser	GGT->AGT

moves more cathodal but very close to HbA[47]. Its presence can only be suspected when it is present as compound heterozygous state by the presence of normal HbA2 level in obligatory heterozygotes[40,47,61]. Additionally, an abnormal ß-chain could be detected by globin electrophoresis in acrylamide gel. Hb Knossos mutation was linked to dC59 (-A) mutation[78,79]. Therefore the lack of an increase in HbA2 level in Hb Knossos heterozygotes would not be surprising. This hemoglobin was reported twice as compound heterozygote with two different ß-thalassemia mutations (Table 5)[40,61].

HbE [beta26 (B8) (Glu->Lys)] is the most common thalassemic hemoglobinopathy in far East and all over the world[3,7,22,23,47]. In Turkey it is seen mostly in Eti-Turks along with HbS with a frequency of 0.16-2.4%[6,7,23]. Electrophoretic mobility of this hemoglobin is similar to that of HbA2[47]. Although it is a ß-chain variant, it comprises 30-32% of the total Hb due to thalassemic effect of the mutation in ß-chain synthesis. Microcytosis and hypochromia are other hematological features of this abnormal thalassemic hemoglobin[47].

Table 5. Abnormal Hemoglobin variants which have been reported in compound heterozygote state with ß-thalassemia

Abnormal hemoglobins	Region	Occurrence	Clinical expression
HbS	Southern Turkey	Common	Severe
HbD/IVSI-110	K. Maraş, Eskişehir*	2 family	Very mild
HbO Arab/IVSI-110	No selection		
HbO Arab/IVSII-1		1 family	Mild
HbE	Çukurova		Mild-moderate
HbE Saskatoon + IVSI-6	No selection	1 family	Mild
HbC/IVSII-745	Antalya	1 family	
Hb Knossos/FSC8	Antalya	1 family	TI
Hb Knossos/IVSI-1	İzmir	1 family	
Hb City of Hope/ß-thalassemia	?		TI
Hb Strumica/ß-thalassemia	Bursa Immigrant Yug	1 family	?
Hb Beograd + BTT	Turkish Immigrant Yug	1 family	Mild

* Unpublished observation of the author.

OTHER ABNORMAL HEMOGLOBINS

A. Abnormal Hemoglobins with HbS Mobility:

The term "HbD" defines several abnormal hemoglobins, which, similar to HbS, have electrophoretic mobilities alkaline pH (Table-6)[19,20,30,47,80]. Differentiation of these hemoglobins from HbS is easily possible by several simple routine tests. However, diagnosis of individual HbD's may pose problems. The quantity of abnormal hemoglobins may give some clue about a or ß-chain variance. ß-chain variants usually comprises of 35-45% of the total hemoglobin. However, coexistence of a-thalassemia with an abnormal hemoglobin of ß-chain results in the reduction in percentage of abnormal hemoglobin. In a^+ thalassemia, the reduction in the quantity of abnormal hemoglobin is minimal and there are no changes in red cell indices. Contrary to this, coexistence of a°-thalassemia with abnormal hemoglobin of ß-chain variant is associated with a reduction in the quantity of abnormal hemoglobin, and hence with microcytosis and hypochromia (Table 7)[47].

a. Hemoglobin S: [ß6 (A3) Glu->Val]

HbS is the most common abnormal hemoglobin in Turkey. It is prevalent in Eti-Turks living in the Çukurova Region that is an Arabic speaking closed population. In various surveys, the prevalence of HbS in this population was found to be between 3-47%[9,21,23,26]. The overall frequency in Turkey is 0.3% and that in thrace is 2.5%. In it is also observed in Manavgat, Antalya. Haplotype analysis of HbS in Turkish patients indicated that the majority of the HbS mutations originates from Western Africa [Haplotype 19 (Benin Type)][18,81]. This haplotype is associated with severe disease, which explains the severe clinical course of sickle cell anemia in Turkey. It is interesting that there

Table 6. Abnormal hemoglobin variants with an electrophoretic mobility similar to that of HbS in pH 8.6 in Turkey

Abnormal hemoglobins	Mutation	Abnormal Hb percentage
HbS*	ß6 Glu-Val	34-38
HbS + a^+-thal*		32
HbS + a°-thal*		20
HbD Los Angeles	ß121 Glu-Gln	35-40
HbG Coushatta	ß22 Glu-Ala	45
Hb Lepore	Fusion Hb	4-15
HbP Nilotic	Fusion Hb	20
HbQ İran**	a75 Asp-His	14-18

* Sickling test is positive,

** Electrophoretic patterns of adult and newborn are different.

Table 7. Abnormal hemoglobins that have been observed in compound heterozygote condition with HbS

Combined abnormal hemoglobins	Region	Occurrence	Clinical expression
HbS/HbD	Wide spread	Several	Mild
HbS/E	Antalya	Rare	Mild
HbS/HbO Arab + a thal		Rare	Mild
HbS/HbO Arab	Thrace	Rare	Mild

are more than 10 ß-thalassemia mutations in compound heterozygotes for ß-thalassemia and HbS (Table 7)[82]. Additionally, in this population red cell glucose-6-phosphate dehydrogenase (G6PD) deficiency is B^- (563T) type[83]. These findings indicate that ß-thalassemia and G6PD mutations had been introduced to a population, which already had the HbS mutation.

b. HbD Los Angeles or HbD Punjab ß121 (GH4) (Glu-Gln)

HbD Los Angeles is the second common abnormal hemoglobin in Turkey. Its overall frequency in Turkey was reported as 0.2% and in Kahramanmaraş region as 0.3[30]. This hemoglobin is, however, present throughout Turkey[19,20,65-67]. HbD Punjab is the major abnormal Hb in Xinjiang Uygur Autonomous Region of China[84]. It is possible that this mutation was introduced to Turkey by Turkoman tribes that migrated to Turkey from Xinjiang area. Presence of this variant in Turkomans living in Erbil (personal unpublished experience of the authors) may support this assumption.

c. The HbQ İran (a75 (EF4) Asp-His)

HbQ İran is an a-chain variants with an electrophoretic mobility similar to HbS. It comprises 18% of the total hemoglobin[16,47]. In the cord blood, a-chain variants may exhibit different electrophoretic pattern than it does in adults because one of the major hemoglobins is the abnormal HbF that is composed of abnormal a-chain and normal gamma chain.

d. Hb Lepore Boston and Hb Nilotic (anti-Lepore)

These two fusion hemoglobins have the electrophoretic mobility of HbD. The amount of abnormal hemoglobin in heterozygote Hb Lepore patients is between 4-14%[34,73,74]. Microcytosis and hypochromia are additional features of Hb Lepore (Table 1d). Although the heterozygote form was reported on several occasions homozygosity has not yet been reported[73,74]. Hb Nilotic was found in a survey conducted in Konya[39,75]. The amount of fusion hemoglobin was 16-21% and hypochromia and microcytosis were not present in this condition[47].

B. Abnormal Hemoglobins with HbA2 Mobility

The list of some of the common hemoglobins with HbA2 mobility is given in Table 8.

a. HbE (ß26 (B8) Glu-Lys) and HbE Saskatoon (ß22 (B4) Glu-Lys)

HbE [ß26 (B8) Glu-Lys] is the third most common abnormal hemoglobin in Turkey. Both HbE [ß26(B8) Glu-Lys] and HbE Saskatoon [ß22 (B4) Glu-Lys] are present In Turkey (Table 1b)[3,6,7,14,22-24,58]. They both move like HbA2 in electrophoresis at alkaline pH (Table 8). In acid agar gel electrophoresis, on the other hand, both

Table 8. Abnormal hemoglobin variants with an electrophoretic mobility similar to A_2

Abnormal hemoglobins	Abnormal Hb percentage	Red cell indices	Agar gel electrophoresis at pH 6
HbC	36-40	NN*	Separates from A and E
HbO Arab	36-40	NN	Separates from A and C
HbE	27-32	HM**	
HbE Saskatoon	40	NN	
HbO Padova	15-18	NN	Cord blood***

* Normochromia, normocytosis,

** Hypochromia, microcytosis,

*** Cord blood electrophoretic pattern is different than adult pattern.

behave like HbA. Therefore, differentiation of these 2 hemoglobins may create some problems. It seems that HbE [ß26 (B8) Glu-Lys] is more common in Eti Turks with a frequency of 0.16-2.4% while HbE Saskatoon was reported in 3 unrelated families living Antalya, Aksaray and Kayseri[71]. One of the subjects was a homozygote. Reports of HbE [ß26 (B8) Glu-Lys] in Turkey date back to a period before HbE Saskatoon [ß22 (B4) Glu-Lys] was discovered. Therefore the diagnosis of HbE needs to be verified using structural analysis. Since HbE [ß26 (B8) Glu-Lys] is one of the thalassemic hemoglobinopathies, percentages of this hemoglobin is lower than HbE Saskatoon [ß22 (B4) Glu-Lys], and microcytosis and hypochromia are accompanying features. These features are usually sufficient to differentiate these two mutations. Recently, HPLC was also reported to be useful for this purpose[47]. HbE Saskatoon [ß22 (B4) Glu-Lys] was originally reported from Canadians of Orkney Island (Scotland) origin[85]. Haplotype analysis indicated that the three Turkish families have a similar founder effect[58]. Haplotype analysis is also required in other populations to claim a similar effect.

b. HbO Arab ß121 (GH4) Glu-Lys

HbO Arab is the fourth most common abnormal hemoglobin in Turkey (Table 1b). It is one of the abnormal hemoglobins that moves like HbA2 at pH 8.6. However, it can be separated from other hemoglobins with similar mobility by acid agar gel electrophoresis (Table 8). HbO Arab was first reported from an Arab but later on was found to be present in Turkey, Bulgaria and Macedonia[47]. Two siblings from Kütahya were found to be homozygous for this variant hemoglobin[68]. Simple heterozygotes and compound heterozygotes were reported from several parts of the country[9,10,34,68,69].

c. Hb Padova a30 (B11) Glu----Lys

HbO Padova is an a-chain variant comprising 18% of total hemoglobin in adults (Table 1a). Although this abnormal hemoglobin moves slightly faster than HbA2 and HbC in adults, abnormal fetal hemoglobin moves slightly slower than HbA2 and HbC [ß6 (A3) Glu-Lys] in cord blood (Table 8)[37].

d. HbC: ß6 (A3) Glu-Lys

HbC [ß6 (A3) Glu-Lys] first was reported from Turkey by Aksoy et al. in heterozygous form. The homozygous form was later reported in one, simple heterozygous form on several occasions, and compound heterozygosity in one subject (Table 1b)[55].

Homozygosity for abnormal hemoglobins: The list of the abnormal hemoglobins reported in homozygous state is given in the (Table 9). Except for sickle cell anemia, hematological and clinical manifestations were mild in the homozygotes[47].

Table 9. Homozygosity for abnormal hemoglobins in Turkey

Abnormal hemoglobins	Region	Occurrence	Clinical expression
HbS/HbS	Çukurova	Common	Severe
	Manavgat		
	Thrace		
HbD/HbD	Tokat and ?*	? rare	Mild
HbO Arab/HbO Arab	Kütahya	1 family	Mild
HbE/HbE	Çukurova and ?*	?	Mild
HbE Saskatoon /HbE Saskatoon	Aksaray	1 family	Mild
HbC/HbC	?	1 family	

*?: Information was not present.

Compound heterozygosity for one of the abnormal hemoglobins and ß-thalassemia mutation and compound heterozygosity for two different abnormal hemoglobins were reported on several occasions. The list of these conditions is given in the Table 5.

As expected, majority of patients has HbS/ß-thalassemia. Due to the severity of ß-thalassemia mutations, clinical and hematological expression of HbS/ß-thalassemia disease is severe in Turkey and the course of the disease is quite similar to that of sickle cell anemia[82]. Contrary to this, due to mildness of ß-thalassemia mutations such as -88 (C-T), -29 (A-G), codon19 (A-G) and IVSI-6 (T-C) clinical expression of the condition is very mild in Africans[86,87]. There is, however, one patient with HbS/IVSI-6 in İzmir exhibiting a very mild course of the disease.

HbS/HbD disease and compound heterozygosity of ß-thalassemia and HbD, HbC, HbE and HbE Saskatoon are all associated with a mild disease[47]. There was mild anemia in HbD/ß-thalassemia associated with IVSI-110 mutation and one patient hemoglobin was high and erythrocytosis was present (unpublished observation of the authors)[67]. HbE Saskatoon/ß-thalassemia associated with IVS-110 mutation resulted in a very mild disorder[14,58].

HbM Iwata alpha87 (F8) His->Arg: Hb Iwate was reported from a large family living in Bursa (Table 1a)[50]. The author restudied from time to time young subjects of this family who are recruited for the Turkish army. This condition in its heterozygous form does not cause any abnormality except for methemoglobinemia. It seems that homozygous form is not compatible with life. Methemoglobin reductase deficiency and HbM may create a problem in differential diagnosis. In a cyanotic patient without any cardiac abnormality, absence of any increase in the methemoglobin level should arise the possibility of HbM. Since there is a dominant inheritance in HbM, family studies may also reveal the presence of similarly affected individuals in the same family[50].

Fast moving abnormal hemoglobins: HbJ Ankara [beta10 (A7) Ala->Asp] is an abnormal Hb of alpha chain that was first reported in a Turkish subject (Table 1b)[57]. It was not found in other screening studies. The a-chain variant of fast moving hemoglobins can easily be differentiated from ß-chain variants by its lower quantity.

HbJ İran ß77 (EF1) His-Asp is a ß-chain variant that is more frequently in Southwest Turkey[41,62]. HbJ Antakya is also a ß-chain variant found in a screening study conducted in Çukurova[38]. HbN Baltimore [beta95 (FG2) Lys->Glu] is a ß-chain variant reported in one subject from Antalya[41].

The list of the other rare abnormal hemoglobins are given Table 1a-f.

Conclusion: The exact number of subjects having abnormal hemoglobins in Turkey is not known basically because there is no national registry for these conditions. In addition, most of the abnormal hemoglobins, even those detected for the first time in a given region, go unpublished. Identification of abnormal bemoglobins used to require elaborative, time-consuming and labor intensive studies such as structural analysis. In the last two decades the introduction of HPLC and DNA studies has helped easy and efficient identification of abnormal hemoglobins. HPLC identifies only known hemoglobins that are included in its program. Detection of unknown hemoglobins requires DNA analysis. There are several centers in Turkey where DNA analysis is possible. A review of abnormal hemoglobins reported from Turkey indicated that in addition to ß-thalassemia major, sickle cell anemia and sickle cell/ß-thalassemia are major causes of public health problems. It is important to note that eradication of these common and devastating conditions are possible by prenatal diagnosis.

Abnormal hemoglobins other than HbS are probably rare because they do not provide any selective advantage for any severe disease. They usually do not create any health problem even in homozygous states. Majority of these hemoglo-

bins was detected in isolated families and does not provides additional information about the genetic make up of the population studied.

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Address for Correspondence:

Çiğdem ALTAY, MD

Department of Pediatrics
Pediatric Hematology Unit
Faculty of Medicine
University of Hacettepe
Ankara, TURKEY