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The Role of Gene Mutations Detection in Defining the Spectrum of ß – Thalassemia in Various Ethnic Regions

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1. Introduction

The thalassemia is a widespread with about 5% of the world population affected by it and is found in some 60 countries, with the highest prevalence in the Mediterranean region, parts of North and West Africa, the Middle East, the Indian subcontinent, southern Far East and south-eastern Asia, together comprising the so-called thalassemia belt. In western countries, thalassemia affects mostly individuals whose ancestry is traceable to high prevalence areas. As an example, there are around 1,000 cases of β-thalassemia major in the United States, most of whom are descendants of Mediterranean, Asian Indian, South Asian or Chinese ancestors. This figure is even less than half of the number of β-thalassemic patients in Fars Province, a region only 120,000 km 2 large in southern Iran (Haghshenas and Zamani, 1997; Rahim et al., 2007). The gene frequency of ß-thalassemia, however, is varies from area to area, having its highest rate of more than 10% around the Caspian Sea and Persian Gulf. The prevalence of the disorder in other areas is between 4-8% (Rahim and Abromand, 2008). There are many genes coding for the globins. They are found on chromosome 11 (β-globin cluster) or chromosome 16 (α-globin cluster) figure1.

1.1 Beta-Thalassemia

Beta-Thalassemia, one of the most widespread genetic diseases in the world, is a common autosomal recessive disorder caused by point mutations in the ß- globin gene that is located as a cluster on the short arm of chromosome 11 (Weatherall et al., 1989; Sack, 1999; Oliveri, 1999). More than 200 different mutations affecting diverse levels of beta-globin genes expression have so far been identified (Trent, 1997; Ho and Thein, 2000). South-western region of Iran also represented various ß-thalassemia mutations (Figure 2). Different strategies of classification individuals genotypes by ß-globin gene cluster and cloning nucleotides sequencing lead to identification of several mutations in Mediterranean (Orkin et al., 1982), Asian Indians (Kazazian et al., 1984, Ohba et al., 1997), American Blacks

(Antonarakis et al., 1984) and Chinese (Cheng et al., 1984). The global distribution indicates a high prevalence in a belt around the earth, which is around the 40th parallel in the Mediterranean area but eastwards moves further south, reaching the equator in Indonesia. More than two million carriers of ß-thalassemia live in Iran. The Iranian populations are mixture of different ethnic groups.
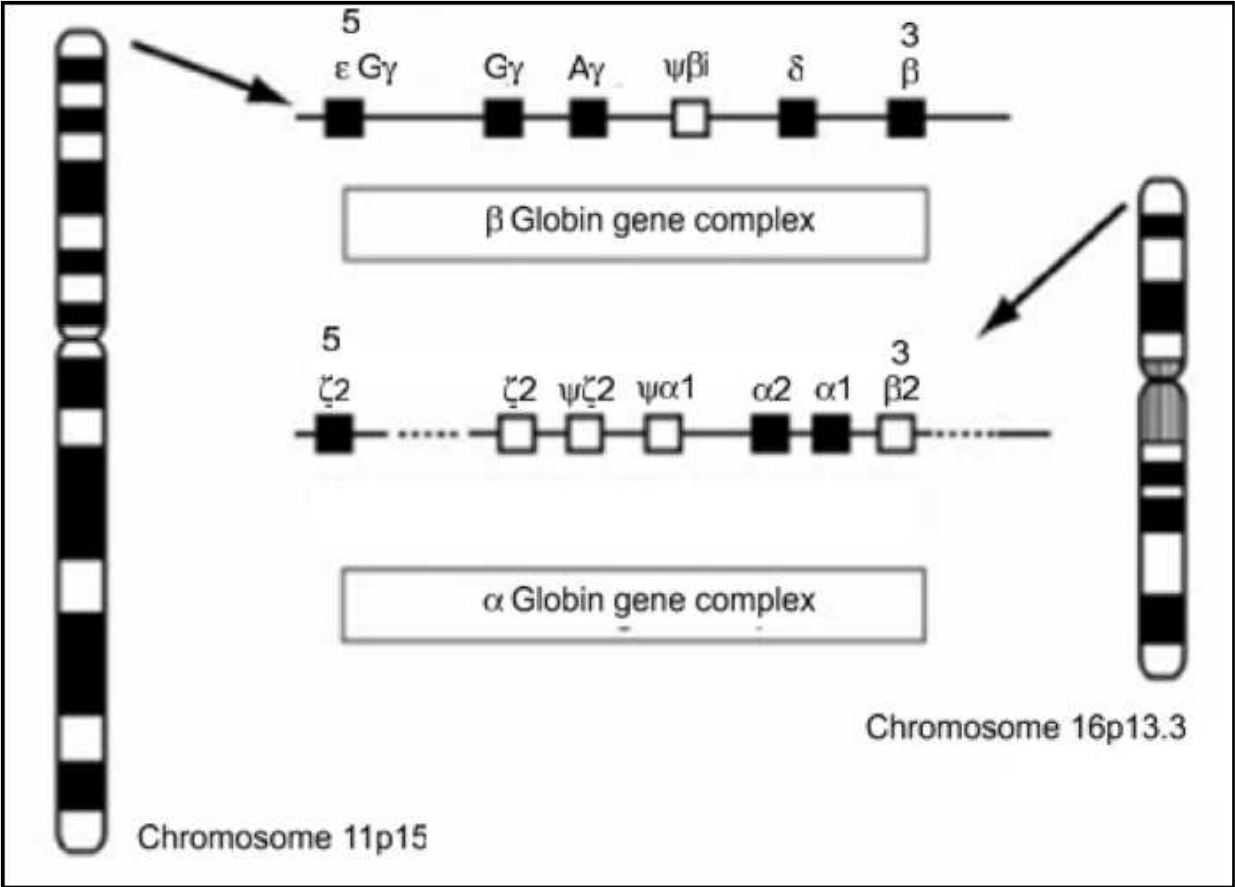

Fig. 1. Two globin gene clusters including α- and β- represented here.

1.2 Alpha thalassemia

Alpha thalassemia disorders are a group of hereditary anemias caused by absent or decreased production of the alpha chain of hemoglobin (Hb) (Vichinsky, 2009). freeAll affected individuals have a variable degree of anaemia (low Hb), reduced mean corpuscular hemoglobin (MCH/pg), reduced mean corpuscular volume (MCV/fl) and a normal/slightly reduced level of HbA2. Molecular analysis is usually required to confirm the hematological observations (especially in silent alpha thalassemia and α-thalassemia trait). A single gene, two-gene, three-gene or four-gene deletions result in alpha thalassemia silent carrier status, thalassemia trait (minor), HbH, and hemoglobin Bart's (Hb Bart's), respectively (Figure 3).
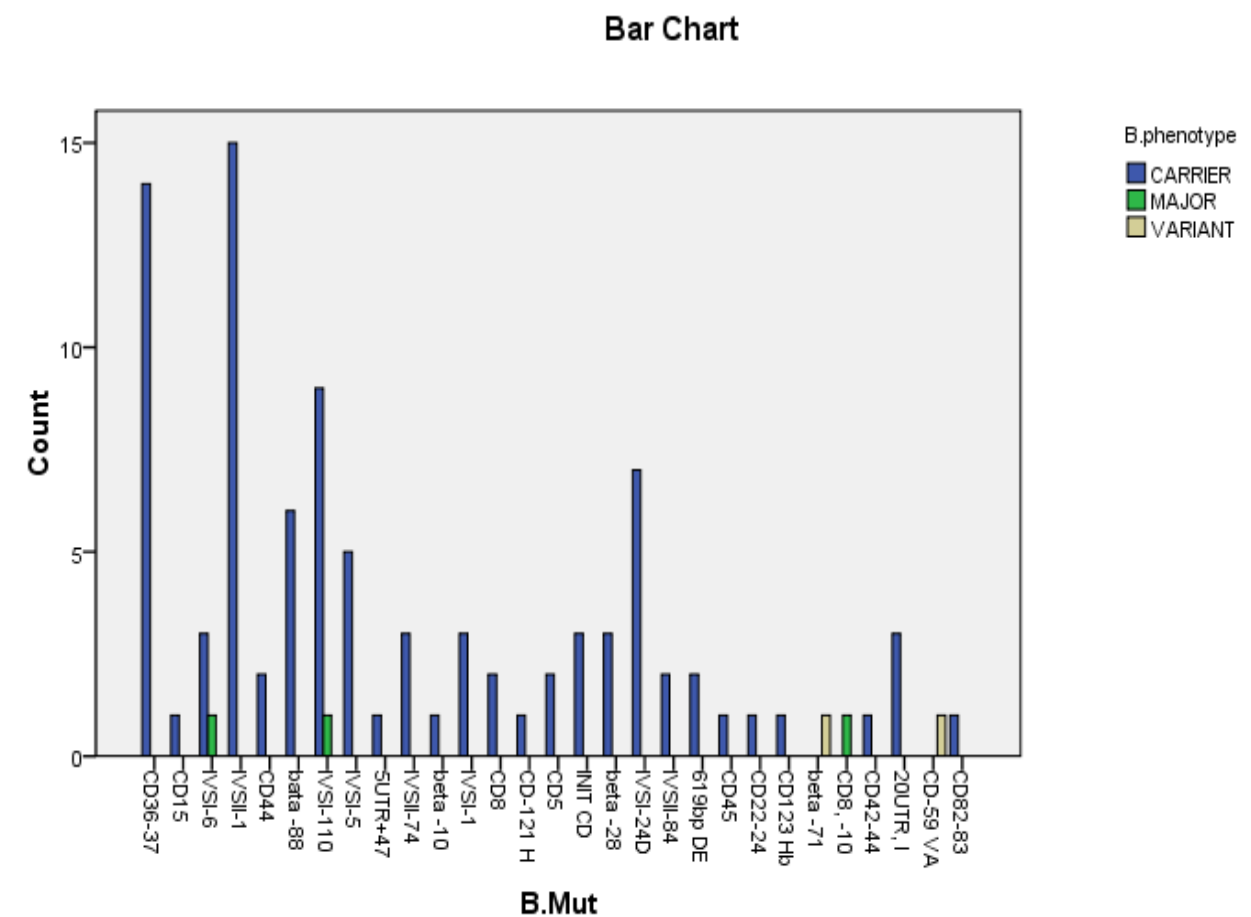

Fig. 2. Different ß-thalassemia mutations detected in our region of study (South-western region of Iran), different explained groups are carrier, which represents the heterozygous type; Major, which represents the homozygous type; Variants, which represents the hemoglobin variants
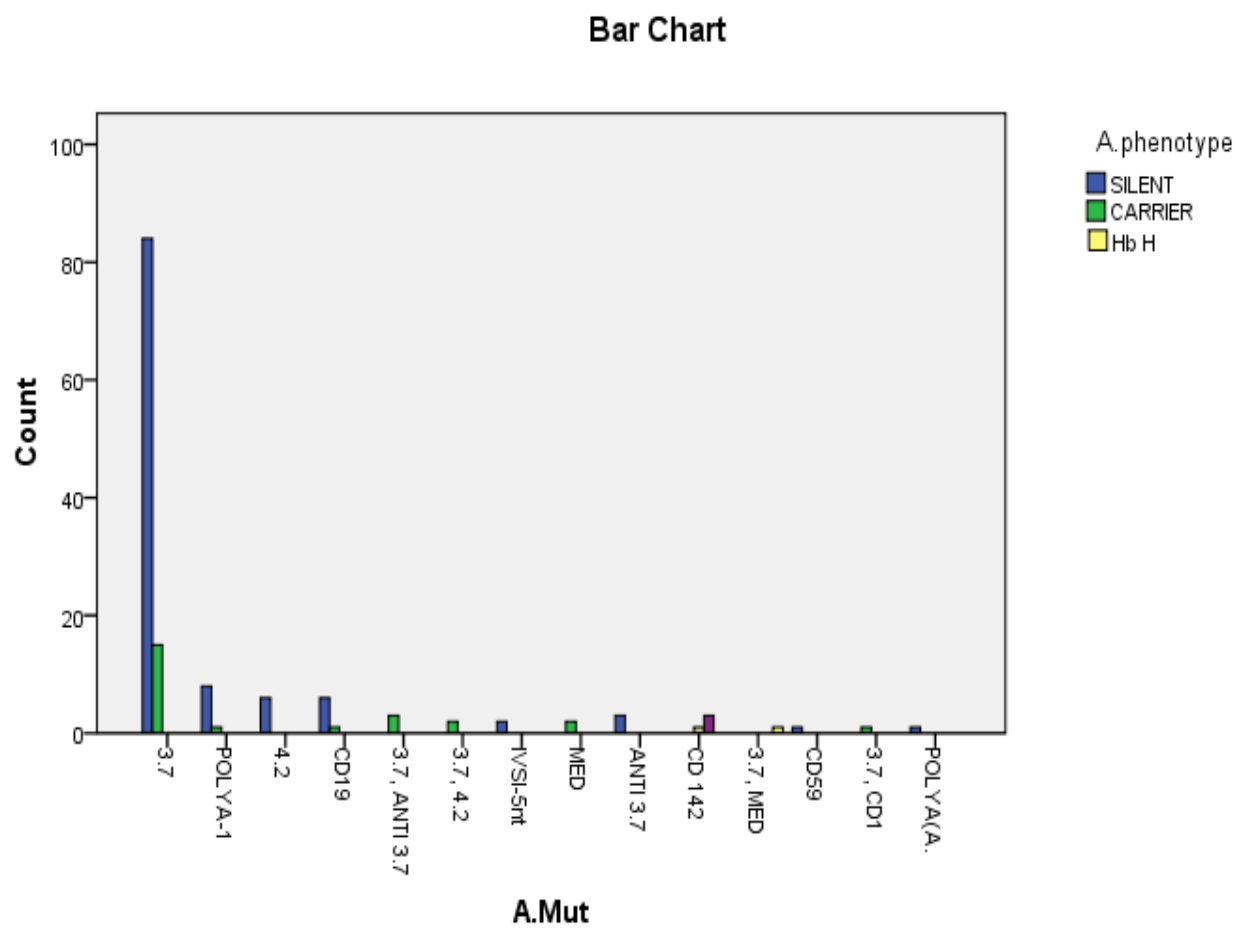
Fig. 3. Different α -thalassemia mutations detected in our region of study (South-western-region of Iran), different explained groups are carrier, which represents the heterozygous type; Major, which represents the homozygous type; HbH, Hemoglobin H disease

1.3 Thalassemia intermedia
Thalassemia intermedia are a clinical phenotype which displays marked genotypic variability in different populations or ethnic groups (Panigrahi et al., 2009). This disorder is a clinical designation often used to characterize individuals who are homozygous for b-thalassemia genes but maintain hemoglobins of 6–9 g/dL without regular transfusions (Galanello et al., 2001). They have more severe RBC morphological abnormalities than the trait, as well as varying degrees of splenomegaly, thrombosis and skeletal changes (Taher et al., 2008).

1.4 Hemoglobin H (Hb H)
Hemoglobin H (Hb H) disease is the most common form of thalassemia intermedia. Hb H (beta4) disease results from double heterozygosity for alpha(0)-thalassemia due to deletions that remove both linked alpha-globin genes on chromosome 16, and deletional alpha(+)-thalassemia from single alpha-globin gene deletions (--/-alpha). However, Hb H disease may occur from interactions between alpha (0)-thalassemia with nondeletional mutations or with abnormal hemoglobins such as Hb Constant Spring, Hb Paksé, Hb Quong Sze, and Hb Pak Num Po (Fucharoen and Viprakasit, 2009).

1.5 Hemoglobin (Hb) Bart's

Hemoglobin (Hb) Bart's hydrops fetalis is a generally fatal intrauterine condition associated with homozygous alpha (0)-thalassemia. It is moderately insoluble, and therefore accumulates in the red blood cells (Karnpean et al., 2009; Singer, 2009).

1.6 Simultaneous α-and β-thalassemia

Some case of complex beta- and alpha-thalassemia coinheritance is described. The chance of finding an individual with co-inheritance of α^0- and β-thalassemia is theoretically 1: 1000. In other words, one in every 25 b-thalassemia carriers co-inherits a^0- thalassemia (Rahim, 2010; Rahim et al., 2008). Routine screening testing, such as mean cell volume (MCV) and Hb A2 level, cannot distinguish double heterozygotes for α and β-thalassemia from the pure β-thalassemia heterozygotes. The α^0-thalassemia can be distinguished simply from double α^0- and β-thalassemia by a normal Hb A2 level (Table 1).

Case	Sex	Age (Y)	Hb (g/dl)	MCV(fl)	MCH(pg)	HbF(%)	HbA2(%)	α-genotype	β-genotype	HbH
1	M	24	13.9	72.1	23.4	1.1	5.3	$-\alpha^{3.7}/\alpha\alpha$	A	-
2	M	32	11.7	70.7	22.6	0.4	5.1	$-\alpha^{3.7}/\alpha\alpha$	B	-
3	M	29	11.4	73.0	22	0.5	5.1	$-\alpha^{3.7}/-\alpha^{3.7}$	C	-
4	F	27	11.9	71.5	22.6	1.5	4.2	$\alpha\alpha/-\alpha^{4.2}$	D	-
5	F	30	10.4	65.0	21	1.4	4.5	$-\alpha^{3.7}/\alpha\alpha$	E	-
6	F	25	11.7	61.4	19.8	0.9	4.3	$-\alpha^{3.7}/\alpha\alpha$	F	-
7	F	23	13.2	69.7	23.2	1.3	5.3	$\alpha\alpha/--_{MED}$	G	-
8	M	29	11.5	75.5	23.2	1.9	4.9	$\alpha\alpha/-\alpha^{4.2}$	H	-
9	M	27	13.3	67.3	22.6	1.4	5.5	$\alpha\alpha/--_{MED}$	I	+
10	M	29	11.1	69.5	23.8	0.9	5.4	$\alpha\alpha/--_{MED}$	J	+

A, $\beta^{IVS 1-5}/\beta^N$; B, $\beta^{IVS 1-25}/\beta^N$; C, $\beta^{IVS 2-1}/\beta^N$; D, $\beta^{CD8(-AA)}/\beta^N$; E, $\beta^{CD121(G-C)}/\beta^N$; F, $\beta^{CD6(CTC-GAG)}/\beta^N$; G, $\beta^{IVS 2-1}/\beta^N$; H, $\beta^{CD121(G-C)}/\beta^N$; I, $\beta^{CD41/42}/\beta^N$; J, $\beta^{CD8(-AA)}/\beta^N$

Table 1. Hematologic and genotypic findings in the 10 double heterozygotes for α- and β-thalassemia

1.7 Co-inheritance of α-and hemoglobin variants

The chance of finding an individual with co-inheritance of α^0- thalassemia with different hemoglobin variants is also presented. In other words, this chance and presentation is rare (Rahim, 2009).

2. Diagnosis

The key to successful detection and characterization of the hemoglobinopathies, particularly the thalassemias, is the initial hematological data. The clue for a thalassemia comes with a low mean corpuscular volume (MCV) or mean corpuscular hemoglobin (MCH). Although

iron deficiency is the other explanation for a low MCV or MCH, it is likely that this finding will point to thalassemia in regions of countries with at-risk ethnic populations (Table 2).

Group(number of cases)	Hb mean ± SD (Range)	MCV mean ± SD (Range)	MCH mean ± SD (Range)
Beta-thalassemia Trait(171)	9.53 ± 1.43 (5.60 - 12.10)	62.9 ± 5.3 (49 - 78.90)	20.03 ± 1.80 (15 - 26)
Beta-thalassemia Major(13)	7.5 ± 1.34 (5.20 - 9.28)	71.6 ± 5.20 (63 - 79)	22.9 ± 2.1 (20.9 - 25.6)
Iron deficiency(42)	7.75 ± 2.05 (4.3 - 12.95)	69.35 ± 6.95 (52.0 - 77.8)	17.52 ± 2.84 (12.10 - 23.12)
Alpha-thalassemia Trait(88)	11.1 ± 1.25 (9.20 - 12.25)	73.6 ± 4.67 (60 - 79)	23.9 ± 1.82 (19 - 26.20)
Hb Variants(11) *	12.1 ± 2.63 (7.8 - 15.20)	73.9 ± 4.4 (66 - 79)	23.5 ± 1.65 (21 - 26.5)

*Includes hemoglobin S (HbS), hemoglobin C (HbC) and hemoglobin DPunjab (HbDPunjab)
Table 2. Hematological parameters in different groups with microcytic hypochromic anemia

2.1 Differential diagnosis of beta-thalassemia

We can differentiate β -thalassemia from other disorders such as iron deficiency anemia with the help of discriminate indices including Mentzer Index, England and Fraser Index, Srivastava Index, Green and King Index, Shine and Lal Index, red blood cell (RBC) count, red blood cell distribution width index (RDWI), Mean Density of Hemoglobin per Liter of blood (MDHL) and mean cell hemoglobin density (MCHD) (Rahim and Keikhaei, 2009). If iron deficiency is present, it is essential to correct this and then repeat the full-blood count and all other investigations. The first step after the initial abnormal blood count is to exclude iron deficiency and if present, to treat it. The blood count is then repeated and if the MCV/MCH remains low, a thalassemia is most likely. Therefore, ferritin levels (and if necessary serum iron, iron binding capacity and percentage saturation) are sought. This is recommended because at times, particularly during pregnancy, it is possible that iron stores will be low or, in the presence of iron deficiency, it is possible that the MCV or MCH are influenced by the iron deficiency. It is also occasionally seen that the HbA$_2$ level can be falsely lowered by iron deficiency. In this context there are special hemoglobin tests which may help in the primary detection scenarios (Table 3).

2.2 Molecular diagnostic methods

Almost all the methods for DNA analysis of the hemoglobinopathies used today are based on the polymerase chain reaction (PCR). Different well-known and applied methods have been described in table 4. Therefore whether a mutation is a deletion, a rearrangement or a point mutation, a similar test will be performed with the variability and specificity coming

Test	What does it measure or detect Y	What does it mean
HbEPG	Electrophoresis of globin proteins. Different techniques possible from gel or membrane-based kits to HPLC. Abnormal bands apart from the usual HbA, HbF and HbA$_2$ peaks can be detected	(1) Gives some idea of the HbA$_2$ level but more importantly (2) identifies if there are any variant Hbs - particularly Hbs such as HbE and HbS.
HbA$_2$	Globin electrophoresis and quantization of the HbA$_2$ peak. Different techniques used from membrane or column-based kits to the more universally suited HPLC are in use.	A raised HbA$_2$ is the key parameter indicating the presence of β-thalassemia. It is said that variant Hbs can raise the HbA$_2$ but this must be a rare event. More of an issue is the borderline normal-raised HbA$_2$ because this might indicate silent β-thalassemia. A low HbA$_2$ is also important to note as this might indicate δ thalassemia
HbF	Globin electrophoresis and quantization with different methods available for the latter.	A slightly raised HbF to 2-3% (normal is <1% in an adult) might indicate heterocellular HPFH or may be a subtle pointer to an underlying silent β-thalassemia. HbF levels 5% and above are more likely to be due to δβ thalassemia or HPFH (heterocellular or pancellular). In the case of δβ thalassemia or deletional HPFH one would expect the HbA$_2$ level to be low.
Kleihauer	Red blood cells are stained to detect HbF. This test is used to distinguish heterocellular from pancellular HPFH.	Not a particularly useful test for distinguishing the types of HPFH because these are very rare and most laboratories are not sure how to interpret the results. The only practical value for a Kleihauer stain might be in fetal blood sampling to confirm that maternal blood has not contaminated a fetal sample (the latter would be homogeneously stained for HbF). Any cells not staining for HbF would represent maternal blood.
HbH inclusions	Red blood cells are stained to detect HbH inclusions (aggregates of β globin protein)	Requires patience and skill to find the HbH inclusions and even with a 2-gene deletion α thalassemia, only 1-2 such inclusions might be found after a search lasting many minutes. There fore, HbH inclusions are easy to miss if the laboratory is inexperienced or the individual looking down the microscope does not spend enough time searching for these inclusions.
Sickle solubility and instability tests	Various tests ranging from biochemical to immunoassay are used to detect HbS and unstable variant Hbs	HbS diseases as well as interactions of HbS with β-thalassemia are increasingly being detected in many Iranian cities. Therefore, efficient and accurate tests for sickling (sickle solubility, HbEPG) are important components of the hemoglobinopathy workup.

Table 3. Special hematologic tests requested once a hemoglobinopathy is suspected based on family history and/or full-blood count.

from the primers used. The sensitivity and specificity of PCR has revolutionized the molecular diagnostic field. It has almost eliminated the use of radioactive isotopes for detecting sequences and has enabled diagnosis to be made on much smaller quantities of DNA. The PCR-based techniques used in hemoglobin diagnostics include allele-specific oligonucleotide (ASO) hybridization or dot-blot analysis, reverse dot-blot analysis, allele-specific priming or amplification refractory mutation system (ARMS), restriction enzyme analysis, amplification created restriction analysis, mutagenically separated PCR and gap-PCR. These PCR-based techniques are useful for identifying a known mutation; PCR-based approaches for scanning or screening for unknown mutations take advantage of altered conformation of single-stranded DNA and include denaturing gradient gel electrophoresis (DGGE), single-strand conformation polymorphism (SSCP) and heteroduplex analysis. The characteristic altered patterns of migration and their position in the scanning methods act as a guide for the location of the mutation, targeting the region for identification by other

means. The ultimate method of mutation identification is by direct sequence analysis of specifically amplified DNA. In the last decade, the use of automated sequencers has led to nonradioactive, more robust and more rapid sequencing, making it suitable as a routine diagnostic tool. Direct sequencing analysis is particularly applicable to the globin genes which are compact and relatively small (1.2-1.6kb) with most of the point mutations within the gene or its flanking sequences (Fakher et al., 2006).

Southern blotting is one of the few non-PCR based molecular techniques that still have a significant role to play in the molecular diagnosis of the hemoglobinopathies. It is very useful in the screening for large deletions or rearrangements and is essential in characterizing novel deletions. The more common deletions can be detected by gap-PCR once the deletion break points have been defined and specific primers flanking the deletion designed. Each of these techniques has its own limitations; the particular repertoire chosen by a laboratory for molecular diagnosis of the hemoglobinopathies depends on the spectrum of mutations encountered in their catchment area and the technical expertise available in the diagnostic laboratory. It is good practice for any DNA diagnostic laboratory to have at least two alternative methods for detecting each mutation (Vrettou et al., 2003).

2.3 Prenatal Diagnosis (PND) & Foetal DNA analysis

Although historically, the prevention program, abortion, was considered unacceptable in Iran, intensive consultation led to the clerical approval of induced abortion in cases with β-thalassemia major in 1997, and a nationwide prevention program with screening, counseling and prenatal diagnosis (PND) network has been developed (Najmabadi et al., 2006 ;Rahim et al., 2007) (Table 4). Many laboratories offering DNA diagnostics of the Hb disorders are also involved in analysis of fetal DNA for the prenatal diagnosis of these disorders. Fetal DNA is usually and preferably, obtained through chorionic villus sampling in the first trimester of pregnancy (10-12 weeks). Chorionic villus sampling provides a good yield of DNA which is isolated using conventional methods of phenol chloroform extraction after careful microscopic dissection to remove any contaminating maternal deciduas. Occasionally, if the sample is too small, it may need to be cultured increasing the risk of maternal contamination. Amniocytes obtained in the second trimester can also be used as a source of fetal DNA but the fetal cells are often contaminated with maternal cells and the results have to be interpreted with caution after analysis for maternal contamination.

Every prenatal diagnosis should be accompanied by copies of haematology results of the parents and prior confirmation of the parental phenotypes and genotypes. The PCR-based techniques that best suit the expertise of the laboratory are then used to screen for the presence of the parental mutations in the fetal DNA. Parental, appropriate positive and negative controls must always be included in the investigations. A limited number of PCR cycles (25-28) should be performed to avoid amplification of any minor DNA species and to minimize amplification of any contaminating maternal DNA. As an added precaution, maternal DNA contamination should be checked for by using polymorphic DNA markers including the variable tandem repeats (VNTRs) such as ApoB and the short tandem repeats or micro satellites. This is particularly important when the fetal genotype is the same as the maternal genotype. Fetal DNA analysis should also be performed in duplicate and confirmed by an independent PCR-based technique. To confirm maternal DNA contamination we used polymorphic DNA markers including the variable tandem repeats (VNTRs) in all cases.

Mutation	Type	Ethnic origin	Heterozygous cases	Homozygote cases	No. of chromosomes (%frequency)
Fr 36/37(-T)	β0	Kurd, Iranian	16	6	28(14.7)
IVS 2-1(G to C)	β0	Iranian	14	7	28(14.7)
CD 6 (Hb S)	βs	----------------	4	9	22(13)
IVS 1-110 (G to A)	β+	Mediterranean	5	5	15(8.8)
IVS 1 –6 (T→C)	β+	Mediterranean	0	5	10(5.89)
CD 44 (-C)	β0	Kurdish	4	2	8(4.7)
IVS 1-5 (G to C)	β0	Asian Indian, SE Asian, Melanesian	2	2	6(3.5)
CD 39(C to T)	β0	Mediterranean	4	0	4(2.35)
Fr 8/9 (+G)	β0	Asian Indian, Japanese	2	1	4(2.35)
IVS 2-745 (C to G)	β+	Mediterranean	4	0	4(2.35)
IVS 1-1(G to A)	β0	Mediterranean	2	1	4(2.35)
IVS 1(3' end)-25bp	β0	Asian Indian, UAE	2	1	4(2.35)
CD 8 (-AA)	β0	Mediterranean	1	1	3(1.8)
CD 5 (-CT)	β0	Mediterranean	2	0	2(1.17)
-88(C to A)	β+	Kurds	2	0	2(1.17)
CD 82/83(-G)	β0	Czech, Azerbaijan	1	0	1(0.59)
IVS 2-2,3(+11, -2)	β+	Iranian	1	0	1(0.59)
IVS 1-130 (G to A)	β0	Egyptian	1	0	1(0.59)
Unknown			23	0	23(14.1)
Total			90	40	170(100)

Table 4. Globin mutations identified by reverse- hybridization and DNA sequencing in 254 thalassemia patient and prenatal DNA sample were initially tested for 22 common mutations by reverse – hybridization (Fakher et al., 2006).

3. Discussion

Iran is a country which has a population with a different ethnic identity and different languages. As we saw mutation in ß-globin gene will lead to thalassemia. Although, all this mutations were found in coastline areas but their geographic distribution has special characteristic properties. In most parts of the world, a small number of thalassemia mutations predominant and the most common ones tend to be those that are geographically the most widespread and presumably also the oldest. For instance, in China and Southeast Asia, four alleles account for 91% of the genes (Kazazian et al., 1986), and in the Mediterranean Basin, six mutation account for 92% of the genes (Najmabadi et al., 2002). However, mutation 619 bp deletion is predominant in India or mutations IVS I-110 and IVS II-1 are most predominant in Arab populations (El-Hazmi et al., 1995). Because of Wars and trade off between different countries in the past years there was exchange of genetic materials between different populations. In one study it show that IVS II-1, IVS I-110, IVS I-1, and CD 8/9. These mutations are the most frequent in Iran and IVS II-1(24%) is most predominant in Khuzestan (Rahim and Abromand, 2008). In a similar work on 1217 patients

with ß- thalassemia the most predominant mutation in North part of Iran was IVS II-1(34%) and in South part was IVS I-5(%) (Najmabadi et al., 2002).

Najmabadi et al (2002), have studied ß -globin mutations and claimed the most common ß -globin mutations is IVS I-130 (G-C), which was identified in six subjects from the North of Iran, three subjects from the Southwest, as well as in one DNA of unknown geographical origin. We have found that most predominant in South was IVSII-I (34%) follows by IVS I-110(15.7%) and CD 8/9(13.3%) (Rahim and Abromand, 2008). Previous research work showed most predominant mutation in Pakistan is IVS I-5(37%) therefore this mutation is most predominant in Sistan-Baloochestan (44.8%)(Southeast of Iran) because it is a neighborhood area to Pakistan (Kazazian et al., 1984). In a work done on thalassemia patients in Hormozgan (Southern part of Iran) claimed that most predominant mutation there is IVS I-5(69%) followed by IVS II- 1(9.6%) (Yavarian et al., 2001).

Research work done in 8 Gulf (Arab) Countries showed that most predominant mutations are IVS I-110 and IVS II-1 followed by IVS I-5, CD39, CD6, IVS I(3' end)-25 bp del (Adekile et al., 2005). Our finding was similar to the work done in Kuwait which showed 6 mutations are most predominant involve IVS II-1, IVS I-6, CD39, IVS I-110, CD8, IVS I-1(all give 64%) and followed by another 2 involve CD44, CD 36/37 (Kurd, Iranian types) that give 10% of the population. We detected different ß-thalassemia mutations in the studied chromosomes and 5 different areas from Iran which showed IVS-II-I (G → A) was the predominant mutation found in all ethnic regions. . The presence of such a high frequency of various local mutants alleles confirms support for a role of non-isolating genetically areas. In likelihood, both founder effect and natural selection caused by migration from neighboring areas have complemented each other to produce the high frequency of unique alleles within each region (Figure 4).
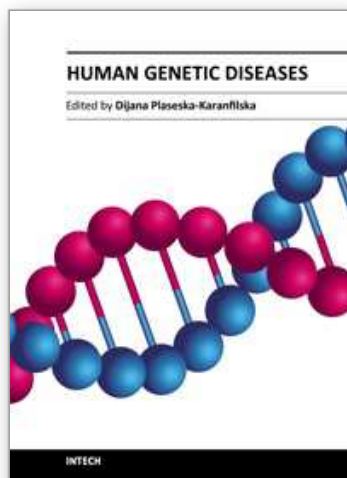

Fig. 5. The origin of mutant alleles with high frequency within different parts of Iran. The most frequent beta-gene mutations in each ethnic region indicated individually.

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Human Genetic Diseases

Edited by Dr. Dijana Plaseska-Karanfilska

The genetics science is less than 150 years old, but its accomplishments have been astonishing. Genetics has become an indispensable component of almost all research in modern biology and medicine. Human genetic variation is associated with many, if not all, human diseases and disabilities. Nowadays, studies investigating any biological process, from the molecular level to the population level, use the â€œgenetic approachâ€ to gain understanding of that process. This book contains many diverse chapters, dealing with human genetic diseases, methods to diagnose them, novel approaches to treat them and molecular approaches and concepts to understand them. Although this book does not give a comprehensive overview of human genetic diseases, I believe that the sixteen book chapters will be a valuable resource for researchers and students in different life and medical sciences.

How to reference

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