Hereditary anemias in Lebanon

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ABSTRACT

The hereditary anemias are a large heterogeneous group of disorders commonly encountered in several populations. This article reviews the occurrence of some forms of hereditary anemias in the Lebanese population. Some of these anemias are relatively more common than others and are characteristic of the ethnic compositions and the geographic situation of the country.

Keywords: Hereditary anemias, Glucose-6-phosphate dehydrogenase deficiency, Thalassemias, Sickle cell anemia, Fanconi anemia.

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The hereditary anemias are a phenotypically and genetically heterogeneous group of disorders affecting mainly the hemoglobin (Hb), red blood cell membrane, enzyme integrity or its functions. These disorders are already making important demands on health resources in developing countries. It has been estimated that these disorders affect over 500 million individuals in the world populations, mostly individuals living in (or coming from) tropical or subtropical countries.[1,2] These high frequencies are found in malaria-infested regions and suggest that heterozygotes carrying the trait of such disorders have parallel mechanisms of protection against *Plasmodium falciparum* malaria.[3-5]

In Lebanon, some of these anemias are relatively more common than others and are characteristic of the ethnic compositions and the geographic situation of the country. This group of disorders includes mainly glucose-6-phosphate dehydrogenase (G-6-PD) deficiency and the hemoglobinopathies.

The physical and human geography of Lebanon. Lebanon is part of the Eastern littoral of the Mediterranean, occupying about 10,500 km^2 with a population of about 3 - 4 million inhabitants. Ethnically, the Lebanese population is composed of a mixture in which Phoenician, Greek, Aramian, and Arab elements are discernible. In Mount Lebanon the dominant strain is related to the Aramians of Asia Minor and the Caucasus region, who must have been driven out of the fertile inland plains and into the surrounding mountain regions by the Semitic invasions. The dominant strain in the coastal towns and in the Beqaa is related to Greeks, the desert-border population of Syria, Persia, Palestine and Arabia and is apparently the same as the Phoenician strain of antiquity. Along with these two major strains are a number of minor ones, representing racial admixtures from East and West and dating from different periods of immigration and invasion.[6-9]

Data about marriage patterns in Lebanon provide evidence for a notable religious endogamy (88%), and isolation of Muslims and Christians, with some migration occuring inside each group.[10] Consanguineous marriages are quite frequent (26%) reaching 40% in some communities. The most commonly encountered type is first cousin marriages (63% of all consanguineous marriages).[10] Consequently, the birth rate of infancts with genetic disorders in Lebanon is quite high.[11] However, for the major types of hereditary anemias, the problem is much more accentuated due to the fact that these mutations have their highest frequencies in regions where malaria is endemic. In the Lebanese history, it was documented that malaria raged throughout the

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Table 1 - The spectrum of ß-thalassemia mutations in Lebanon [number of chromosomes (% of genes)]

Mutations/References	23	25	26	27	Total
IVS-I-110 (G-A)	31 (62)	4 (28.7)	20 (66.7)	44 (40)	99 (48.5)
IVS-I-1 (G-A)	-	1 (7.1)	-	19 (17.3)	20 (9.8)
IVS-I-6 (T-C)	4 (8)	2 (14.3)	2 (6.7)	6 (5.5)	14 (6.9)
IVS-11-1 (G-A)	-	1 (7.1)	1 (3.3)	9 (8.2)	11 (5.4)
Cd 29 (C-T)	4 (8)	-	-	4 (3.6)	8 (3.9)
FSC-5 (-CT)	-	2 (14.3)	-	5 (4.6)	7 (3.4)
FSC-8 (-AA)	3 (6)	-	-	4 (3.6)	7 (3.4)
IVS-II-745 (C-G)	2 (4)	-	1 (3.3)	4 (3.6)	7 (3.4)
IVS-I-5 (G-C)	2 (4)	-	-	3 (2.7)	5 (2.4)
Cd 39 (C-T)	2 (4)	-	1 (3.3)	-	3 (1.5)
-88 (C-T)	-	2 (14.3)	-	1 (0.9)	3 (1.5)
290 bp del	-	-	-	3 (2.7)	3 (1.5)
IVS-II-1 (G-T)	2 (4)	-	-	-	2 (1.0)
FSC 44 (-C)	-	-	-	2 (1.8)	2 (1.0)
Cd 30 (G-A)	-	-	-	2 (1.8)	2 (1.0)
IVS-I-,-1 (G-C)	-	1 (7.1)	-	-	1 (0.5)
-87 (C-G)	-	-	-	1 (0.9)	1 (0.5)
-30 (T-A)	-	-	-	1 (0.9)	1 (0.5)
25 bp del (Iranian)	-	-	-	1 (0.9)	1 (0.5)
-86 (C-G)	-	1 (7.1)	-	-	1 (0.5)
Undetermined	-	-	5 (16.7)	1 (0.9)	6 (2.9)
Total	50 (24.5)	14 (6.9)	30 (14.7)	110 (53.9)	204 (100)

country except in the central parts, the cities of Beirut and Tripoli, and high up in the mountains. The most marshy areas were the littoral, especially the Akkar plain, south Lebanon, and the Beqaa plain.[12] This accounts for the high prevalence of the most common hereditary anemias in the communities living in these regions.

Glucose-6-Phosphate Dehydrogenase Deficiency. Glucose-6-Phosphate Dehydrogenase (G-6-PD) deficiency, the most common type of red cell enzyme defects, is mainly caused by a profound shortage of the enzyme G-6-PD in red blood cells as well as in phagocytes. It is the most common enzymopathy affecting approximately 400 million people worldwide.[1] The most common clinical manifestations are neonatal jaundice and accute hemolytic anemia. The latter can be triggered by a number of drugs, by infections, or by the ingestion of fava beans (an important ingredient of the Lebanese cuisine).

The frequency of G-6-PD deficiency is estimated at 3.1% in Lebanon. In a study conducted in 1964 on 549 Lebanese male blood samples,[12] Taleb et al, concluded that the disorder is present in many of the ethnic groups in the country except in the Druze and Aramians. Most likely, this is due to the fact that these groups used to live in the areas which were not infested by malaria. Since G-6-PD deficiency is considered to be a mutation surviving in the regions where malaria is endemic, these groups, thus, had no reason, evolutionary speaking, to develop or maintain the mutant trait.

In a recent study conducted at the molecular level,[13] Kurdi-Haidar et al examined 21 unrelated Middle Eastern individuals with G-6-PD-Mediterranean (named as such because it is a variant found in different populations around the Mediterranean Sea). The only Lebanese patient studied, was found to have the 563 mutation, which is a single C-T transition causing a serine phenylalanine replacement at amino acid position 188. In addition to that, a silent C-T change at nucleotide 1311 was also described in the same patient. This result was in accordance to what was observed in the majority of the other studied patients. This fact, caused Kurdi-Haidar and colleagues to conclude that most Middle Eastern subjects with the G-6-PD-Mediterranean phenotype have the same mutation as that found in Italy, and that the silent mutation is an independent polymorphism in the Middle East, with a frequency of about 13%. The mutation leading to G-6-PD-Mediterranean deficiency probably arose on a chromosome that already carried the silent mutation. These finding suggested that the G-6-PD-Mediterranean mutation might be quite ancient and that its primary origin might have spread in the Mediterranean area along with the Greeks,[14] from whom most of the populations residing in the coastal towns of Lebanon have originated.[9]

ß-Thalassemia. ß-Thalassemia is an autosomal recessive disorder characterized by microcytosis and hemolytic anemia, and by diminished "$ß^+$-thalassemia" or absent ($ß^0$-thalassemia) ß-globin chain synthesis.[15] Twenty years after the first description of thalassemia by Cooley and Lee,[16] cases

of thalassemia started being diagnosed in Beirut on the basis of physical and radiological examinations and blood tests. Later on, Cabannes and colleagues[17] published a study on hemoglobin types and the frequency of ß-thalassemia trait in the Lebanese population. The mean frequency of ß-thalassemia trait was calculated to be 2-3%.[17] However, in that study it was mistakenly concluded, as shown by the most recent clinical observations,[18] that the highest density of thalassemia was found in the Druze. Until the end of the 1960s, however, only a few cases of ß-thalassemia were diagnosed[19] since the city of Beirut had only two research centers. The populations affected and living in backward regions far from these centers did not know of the correlation between their anemia and endemic malaria,[20] moreover, a large group (70%) had not heard about the disease and its inherited nature before having an affected child.[21] Consequently, thalassemic children were taken to general practitioners, who treated them for iron-deficiency anemia. These patients were underdeveloped, confined to the house and died young.[20] Those in whom ß-thalassemia was diagnosed, had treatment that generally was far from adequate; securing desferrioxamine and paying for follow up visits to the doctor appeared to be the most important financial burdens because the majority of the families came from a low socioeconomic level and had a high birth rate.[21]

However, it was shown that most of the families favoured the idea of prenatal diagnosis in any subsequent pregnancy and nearly 50% of them decided that they would terminate an affected pregnancy.[21] In 1994, Lebanon witnessed a well-designed campaign which was launched as preliminary public accentuation against ß-thalassemia. As a result, the idea of the "Chronic Care Center" crystallized. Since that date, a number of medical and preventive activites were accomplished. Today, the center is taking care of 416 patients with ß-thalassemia, providing them with regular medical follow-up, nursing care, social assistance and psychological support. In addition, infusion pumps, blood transfusion, Desferal and other medicine are offered free of charge.

Molecular studies concerning ß-thalassemia in Lebanon started conflicting with a publication of Chehab and colleagues[22] regarding data about the globin synthetic ratios in 23 Lebanese homozygous ß-thalassemia patients and the presence of both the $ß^0$-(22%) and $ß^+$-forms (78%) of the disorder in the country. However, a much more advanced achievement came along with a report about the first successful prenatal diagnosis case for ß-thalassemia in the Lebanese performed at the University of California, San Francisco, USA, by Chehab et al who also presented a study about the molecular basis of ß-thalassemia in Lebanon.[23] This study revealed the presence of eight different mutations in 25 patients. In 1990, a novel C to G change at position -86 of the ß-globin gene promoter region was reported in a Lebanese patient.[24] Recently, three studies on a number of chromosomes from patients of Lebanese descent living in Canada,[25] Saudi Arabia,[26] and Lebanon[27] were carried out. In these studies, 11 additional mutations not previously described in

Table 2 - Frequencies of ß-thalassemia mutations in Lebanon and in some of its neighbouring countries (% of genes)

Mutations	Turkey	Cyprus	Lebanon	Syria	Egypt	Jordan
IVS-I-110 (G-A)	39.3	79.7	48.5	44.4	36.5	26.9
IVS-I-1 (G-A)	5.0	5.9	9.8	16.7	12.6	6.2
IVS-I-6 (T-C)	10.1	6.2	6.9	-	14.5	6.2
IVS-11-1 (G-A)	4.7	-	5.4	2.8	4.4	16.2
Cd 29 (C-T)	-	-	3.9	-	-	-
FSC-5 (-CT)	2.2	-	3.4	-	1.3	2.3
FSC-8 (-AA)	5.5	0.2	3.4	-	1.3	-
IVS-II-745 (C-G)	5.0	5.5	3.4	16.7	4.4	10.0
IVS-I-5 (G-C)	1.1	-	2.4	-	-	3.8
Cd 39 (C-T)	3.8	2.4	1.5	11.1	1.3	1.5
-88 (C-T)	-	-	1.5	-	-	-
290 bp del	-	-	1.5	-	-	-
IVS-II-1 (G-T)	-	-	1.0	-	-	-
FSC 44 (-C)	1.3	-	1.0	-	-	-
Cd 30 (G-A)	-	-	1.0	-	-	-
IVS-I-,-1 (G-C)	-	-	0.5	-	-	-
-87 (C-G)	0.8	-	0.5	-	-	1.5
-30 (T-A)	3.1	-	0.5	-	-	-
25 bp del (Iranian)	-	-	0.5	-	-	-
-86 (C-G)	-	-	0.5	-	-	-
Others	18.1	0.1	2.9	8.3	23.7	25.4
References	*	28	23, 25-27	26, 29, 30	26, 29, 30	26, 31

*Tadmouri et al unpublished observations.

Lebanese, were observed.

By compiling all of the known information about the molecular basis of ß-thalassemia in Lebanon (Table 1), it can be easily noticed that this population carries a wide array of different mutations. Interestingly, most of these mutations occur in the same order of prevalence as in neighbouring countries (Table 2). This fact can be explained by the history of the country which has long been a crossroads of several civilizations. However, some mutations appear to be more prevalent in Lebanese. For example, the Cd29 (C-T) mutation was found to be carried by 3.9% of Lebanese ß-thalassemia patients. This mutation has not yet been reported to occur in any other population with such a high incidence. To our knowledge, three chromosomes from Azerbaijan[32] and one from former Yugoslavia[33] were said to be carrying this mutation. It should also be noted that the majority of affected individuals were reported as homozygotes for single ß-thalassemia mutations, including rare ones. This is probably due to the considerably high consanguinity rate in the Lebanese population.[25]

Sickle Cell Gene. In 1965, a study was undertaken with the aim of surveying the different types of hemoglobinopathies in the population of Lebanon.[17] In that survey, which included 3,000 individuals, nine were described to be carrying the HbS trait (ie. 0.34%). These included four Shiites, three Sunnites, one Maronite, and one Greek Catholic. Although the study did not reveal a real value of the occurence of the trait in the country, no cases were found among Greek Orthodoxes, Druzes or Armenians, as expected. However, in an earlier investigation,[34] Aksoy showed a frequency of 4% sickling among the Allewits school children in Tripoli, Lebanon. He also pointed out that the Allewits of Syria and Lebanon may have the same racial background as the Eti-Turks, and Arabic speaking population living in South Eastern Turkey. In a review of a 10-year experience in the Pediatric Hematology Clinic of American University Hospital in Beirut,[35] almost equal number of admissions from Muslim and Christian patients were seen. The subjects were nationals of different Arab countries, the majority were, however, Lebanese. It was noticed that the sickle cell trait was present in nearly all patients from Muslim communities. In that same report, the sickle cell gene was observed in the homozygous state (51%), in the heterogous state (34%), and in association with thalassemia (HbS/thalassemia; 15%).[35] In a second study on the hemoglobinopathies in Lebanon, however, seven more cases of sickle cell anemia along with two cases of HbS/thalassemia were reported.[19]

Although reports on the, presence of sickle cell gene in Lebanon came to light later than those dealing with, ß-thalassemia, their considerably small number should not be underestimated. Confidently, it can be said that the sickle cell trait is relatively common in the country with an overall frequency estimate of 1% and an expectancy of 6-29 cases per 100,000 births for the HbS homozygotes and HbS/thalassemia, respectively.[36] The relatively high number of births of patients with HbS/thalassemia can be due to the high frequencies of both genes in the country. As for HbS, this is probably because Lebanon is situated on one of the belts with a relatively high occurrence of the gene, extending from Northwestern Africa (1%),[36] through Saudi Arabia (l-18.7%),[37] and reaching the South Eastern part of Anatolia or Asia Minor (0.3-37%).[38] Consequently, the Eastern Mediterranean coast, including the Lebanese littoral, is a strong candidate to harbor this disorder. It is commonly accepted to say that Lebanon witnessed a continuous genetic flow from the different races, mainly Muslim populations, who resided in that belt and migrated to settle in the country during the last 14 centuries. Hence, the majority of today's Lebanese population are genetically related to communities residing in that belt.[7,9]

α-Thalassemia and HbH Disease. Very little is known about the occurrence of either a α-thalassemia or HbH disease in Lebanon. The Lebanese documents report the encounter of HbH disease in only one instance. The disorder was described, almost 20 years ago, in an extended Sunnite Moslem family which originated from a small village in Southern Lebanon.[39] In this family, four sibs (three males and one female) had typical HbH bands on electrophoretic examination, and characteristic intracorpuscular inclusion bodies were demonstrated in a variable proportion of their erythrocytes, as well

Table 3 - G-6-PD deficiency, ß-thalassemia, and HbS gene frequencies among different religious groups from Lebanon[12,17,19,34,48]

	Shiites	Sunnites	Maronites	Orthodox	Catholic	Druze	Latin	Alewits
ß-thalassemia	5-7%	6-9%	1-2%	0.2-0.6%	0.4-0.5%	0.3-0.9%	<0.1%	?
HbS	0.6-0.7%	0.5-0.6%	0.1-0.2%	0.1-0.2%	-	-	-	4%
G-6PDD	3-4%	3-4%	2-3%	<2%	<2%	-	-	?

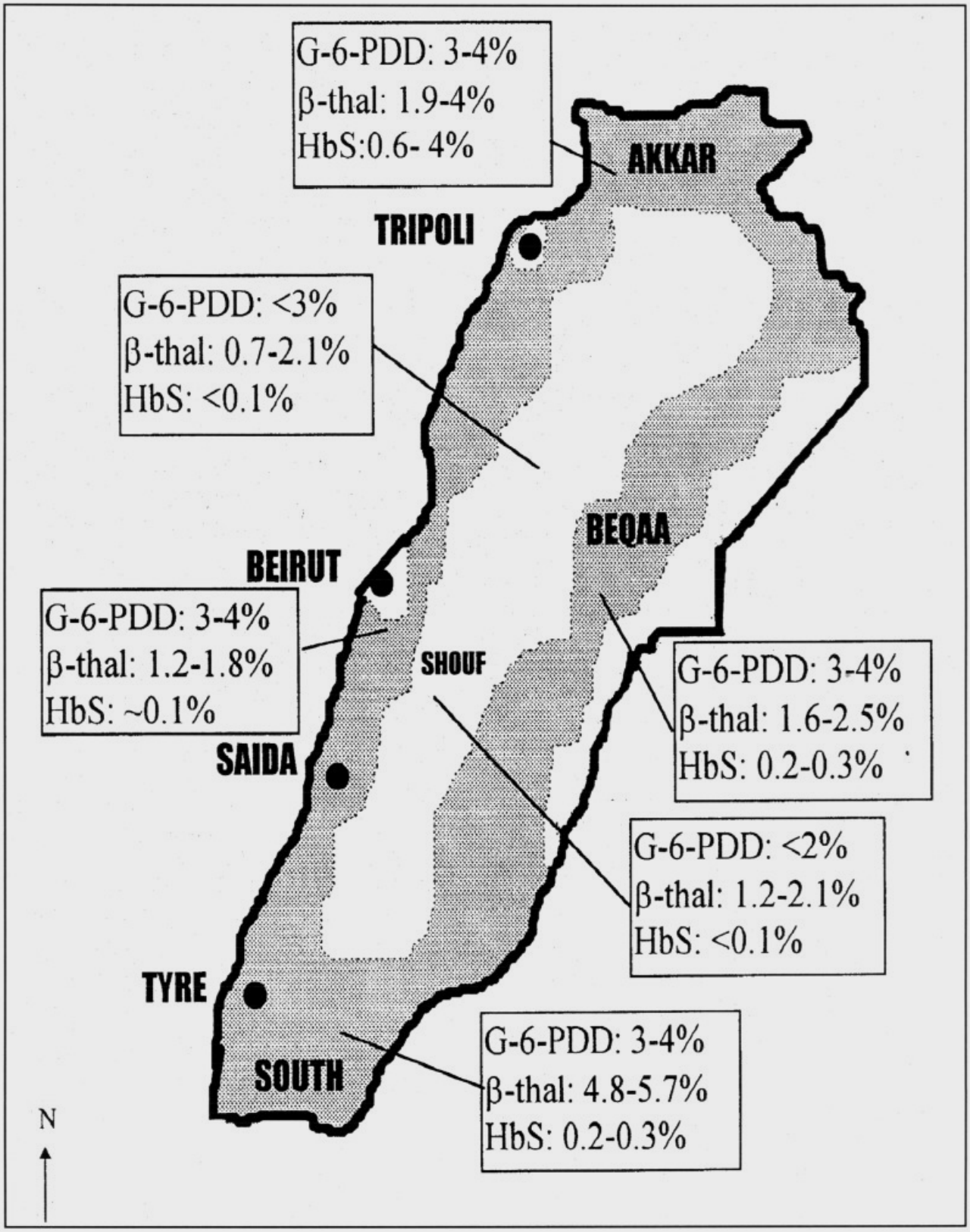

Figure 1 - G-6-PD deficiency, ß-thalassemia, and HbS gene frequencies in different regions of Lebanon[12,17-19,34,48]

as in cells from a younger sib and from the mother. The latter also had elevation of the HbA^2 fraction, and it suggested that she had a combination of ß-and α-thalassemia.[39]

Only one α-thalassemia case was reported in the Lebanese population. The subject, a carrier mother, showed the inheritance of the -88 (C-T) mutation of the ß-globin gene (as a trait) along with a deletion of 3.7 Kb in one of her ß-globin gene copies ($-\alpha^{-3.7}/\alpha\alpha$).[25]

From the information presented so far, it is noticed that there is no well established knowledge about the frequencies of α-thalassemia and HbH disease in Lebanon. However, this does not lead to the conclusion that such disorders are not highly frequent in this country. On the contrary, many reasons make it possible to suggest the common presence of α-globin gene defects in Lebanon. In a recent review about α-thalassemia in Saudi Arabia, it was reported that the frequency of occurence of all forms of the disorder ranged between 1 and 47%.[37] Increasing number of cases have also been recorded so far in Turkey (Basak, A.N., personnal communication, Istanbul, 1998). Leaning on the historical facts proposing the flow of populations from these countries towards Lebanon during the last centuries,[7,9] it is plausible to say that the disorder may be quite established in Lebanon as well. The coinheritance of both forms of thalassemias (i.e. ß and α) in some patients[39,25] (personnal observations) may also give more strength to the theory of the high incidence of α-thalassemia. Learning the exact figures, however, requires wide investigations in order to define the different aspects of the disorder in Lebanon.

Hemoglobin variants. To date, there are no reports in Lebanon about cases of anemias caused by the inheritance of a mutation leading to the production of an abnormal hemoglobin. To our knowledge, the only published study so far, reported the presence of a neutral substitution of alanine for valine at position 126 in the ß-chain of hlemoglobin[40] detected by reverse-phase high-performance liquid chromatography (HPLC).[41] The variant (named HbBeirut) was detected in an adult male of Lebanese extraction and in both his mother and sister. However, none of the three individuals was anemic or exhibited any abnormal hematological features.[40] The authors speculated that the absence of hematological abnormalities in these individuals may be due to the fact that the valine at residue 126 occupies a surface crevice of the hemoglobin α-helix and is not involved in interchain or heme bonding.

Fanconi's Anemia. The persistence of fetal hemoglobin formation after infancy is usually taken to indicate an anemic state existing from early life and is most commonly found in association with hereditary hemoglobinopathies. A further example of such a form of anemia has been found in patients suffering from Fanconi type anemia.[42-44] This disorder is inherited as an autosomal recessive condition that affects all three hematopoietic lineages and is characterized by pancytopenia with strikingly elevated levels of hemoglobin F.[45]

In Lebanon, only one case of Fanconi's anemia has been described so far.[46] In the patient reported, a young male, 10% of the bone marrow cells were shown to have significant chromosomal abnormalities. Breaks involving primarily groups B and C members constituted the most frequent changes encountered, while some cells had either a dicentric or a ring chromosome. In that study it was suggested that in this disease chromosome breakage is a process *in vivo*, and that its occurrence in bone marrow cells possibly contributes to their progressive elimination and ultimate depletion.[46]

Since there are no other reports about the occurence of the disorder in Lebanon, figures about the incidence of its gene and its distribution in the different Lebanese communities remain unknown.

Conclusion. The Lebanese population is composed of numerous ethnic, religious, and kinship groups which developed from the successive settlements of neighbouring populations. This fact, as well as the practice of consanguineous marriages in Lebanon, contribute to a large extent to the presence of all 117 genetic disroders described in Lebanese,[47] of which the hereditary anaemias are the most common due to strong malarial selection (Figure 1, Table 3). In this review we have outlined the most important achievements done in Lebanon concerning the studies on hereditary anemias. It is noticed that during the period between the years 1975 and 1992, research in Lebanon went into a bottle-neck due to the war which raged throughout the country. However, this situation seems to be resolving as realized from the growing number of papers published from Lebanon in recent years.

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