

Review synthetic Report

Synthetic review on the different anthropological aspects of hemoglobinopathies in Tunisia

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Abstract - Hemoglobinopathies are a group of hereditary hemolytic anemia characterized by qualitative (sickle cell disease) or quantitative (thalassemia) defects in the alpha or beta-globin chain synthesis. Homozygotes or compound heterozygotes for the mutated alpha or beta-globin genes can cause severe anemia at an early age. These pathologies are common in some areas (Mediterranean, Africa, India, and Southeast Asia). Tunisia, by its geographical location, its history and its socio-economic system, is particularly concerned by these pathologies. The frequency and severity of the beta-thalassemia syndrome justify the establishment of prevention programs including screening and genetic counseling especially in regions with relatively high degree of consanguinity. Molecular investigations are conducted to identify the molecular defects involved in β -thalassemia. Determination of the spectrum and distribution of beta globin gene mutations and haplotypes associated gave us the opportunity to develop and improve diagnostic tests and eventually to offer ante-natal diagnosis. In addition, molecular analyses gave us important anthropological information about the origins and the spread of Hemoglobinopathies mutations. Investigations have been conducted to propose the origin and the migration schemes of the most frequent β -thalassemia mutations in Tunisia (codon 39 and IVSI 110): a west-Mediterranean and ancient origin for codon 39 and an east-Mediterranean origin (Anatolia) for IVSI 110 during the Neolithic period. Concerning the β S mutation of the sickle cell anemia, the β -globin cluster restriction enzyme haplotypes and the sequence polymorphism analyses show a multicentric origin for this mutation. Arose about 3,000 years ago, this mutation was very likely introduced in North Africa from sub-Saharan Africa.

Key words: Hemoglobinopathies, Genetic counseling, Molecular analyses, Migration schemes, Origins of mutations.

Introduction

The relationship between anthropology, medicine and medical practice is well documented (Comelles and Martínez-Hernández, 1993). General anthropology has a key position in the field of medical sciences. Medical anthropology studies "human health and disease, health care systems, and biocultural adaptation (McElroy, 1996). It integrates humans in multiple perspectives (McElroy and Townsend, 1989). It is one of the most highly developed areas of applied anthropology (Seymour-Smith, 1990) and is a subfield of social and cultural anthropology that examines the ways in which culture and society are organized around or influenced by health, healthcare and related fields.

Medical anthropology emerged from genetic anthropology for interesting particularly to beliefs and rituals related to health and their possible relation to biological variation in humans. Today, medical anthropologists are interested in a wide range of topics, including the cultural foundations of health, disease distribution, beliefs and practices related to health, diagnostic process and choice of treatment.

In this paper, we provide an anthropological approach in the analysis of hemoglobinopathies in Tunisia. Knowledge of the molecular defects and haplotypes associated with these defects allows the development and improvement of diagnostic tests and the management of these diseases. In addition, it helps us to understand the origins and the migration schemes of these mutations in the Mediterranean area.

Hemoglobinopathies are a group of inherited hemoglobin diseases. They are defined by qualitative and/or quantitative abnormalities affecting the globin chains (Weatherall and Clegg, 1981). To date, more than 700 β -globin gene mutations have been described (Hardison et al, 2002, Patrinos et al, 2004). Qualitative abnormalities lead to the production of an abnormal structure of Hb. Among these variants, the best known are HbS causing sickle cell disease, HbC and HbE, mostly because of the biological consequences they generate. However, the majority of variants is asymptomatic and therefore remains unknown. Hemoglobin quantitative abnormalities result from either the reduction or the absence of synthesis of α - or β -globin chains. They define the α -thalassemias and β -thalassemia, respectively.

Epidemiological data

Initially described in the subtropical regions and the Mediterranean Basin, hemoglobinopathies are now spread all around the world especially because of migration. Tunisia, by its geographical location as a migration crossroad, its history and its socioeconomic and cultural system (relatively high degree of consanguinity) is one of the interesting geographic hot-spots.

The high frequency and clinical severity of hemoglobinopathies make them a major public health problem mostly in Africa due to the limited resources available for the management and prevention of these diseases. Despite considerable advances in the control and management of the hemoglobinopathies, therapeutic approach and follow up remain problematic because of the major economic and organizational difficulties in the developing countries. In sub-Saharan Africa, for example, problems are majored by social and cultural environment including infection and malnutrition state (Fattoum, 2009).

Moreover, the selective pressure of *Plasmodium falciparum* in regions endemic for malaria has increased the frequencies of the α and β mutated genes (Flint et al, 1986). Indeed, sickle cell disease provides the best example of a change in the hemoglobin structure that impairs malaria growth and development. The initial hints of a relationship between both the diseases came with the well documented proofs that the geographical distribution of beta globin S (β S) allele overlaps the distribution of malaria in Africa.

Sickle trait provides a survival advantage over people with normal hemoglobin in regions where malaria is endemic. People (and particularly children) infected with *P. falciparum* are more likely to survive the acute illness if they have sickle cell trait. Thus, natural selection occurs with the allele for sickle hemoglobin in areas endemic for *P. falciparum* malaria. People with two genes encoding normal hemoglobin HbA have a significant chance of dying of acute malarial infection in childhood. In contrast, homozygous HbS state is lethal at an earlier age. People with sickle cell trait are more likely to survive their initial acute malarial attacks than are HbA homozygous people. Also, they suffer none of the morbidity and mortality of sickle cell disease.

Therefore, the people with sickle cell trait are more likely to reach reproductive age and to transmit their genes to the next generation (Ringelmann, 1976). This genetic selection called "balanced polymorphism" is a scenario in which a heterozygote has an advantage over either of the homozygous states. The same balancing selection has been described for G6PD deficiency which is thought to provide reduced risk from infection by the Plasmodium parasite (Tishkoff et al, 2001; Verelli et al, 2002).

Among the abnormal HbS, sickle cell disease is by far the most frequent one. It affects mostly people from Africa, Madagascar, Reunion and Caribbean islands, Central America, the Mediterranean Basin and the Middle East (Galactéros, 1995). In Tunisia, the average frequency of the disease is 1.89 % (Fattoum, 2009). Beta-thalassemias are frequently observed in subjects from the Mediterranean area (Italy, Sardinia, Sicily, Greece, North Africa), but they are also found in patients coming from Africa and Asia (Iran, India, Vietnam, Thailand) (Rosa et al, 1993). In Tunisia, β -thalassemias reached 2.21 % (Fattoum 2009). The α -thalassemias, however, are found mainly in populations of Southeast Asia (Cambodia, Laos, Myanmar) (Fuchaoren, 1987) but also in the Mediterranean Basin and Central African countries (Rosa et al, 1993). In Tunisia, α -Thalassemias show an incidence of 4.8 to 5.48 % (Fattoum 2009).

In light of this epidemiological presentation, we can note the need to reconsider precisely how to implement to improve the care of patients. These resources must be focused on improving the quality and quantity of hematological services, the upgrade of their diagnostic tools, and a better availability of prevention and treatments.

Screening and genetic counseling

The fruitful collaboration of obstetricians and hematologists allowed the performance, in a few years, of a significant number of tests, with better reliability and increased security. Effective prevention programs have been carried out in the regions concerned by hemoglobinopathies. Prevention should remain the major priority of health services to reduce the incidence of these diseases. Programs of systematic screening of hemoglobinopathies by phenotype analysis were established for subjects at risk. The screening for β - and α -thalassemia is based on the clinical presentation of these disorders. A relatively common approach is the execution of blood count to assess the mean cell volume and the mean cell hemoglobin.

The finding of normal MCV (mean corpuscular volume) together with normal MCH (mean corpuscular hemoglobin) can rule the most cases of thalassemia and ensures that no further screening for thalassemia is needed. For people whose MCV < 80 fL or whose MCH < 27 pg, the next step is a hemoglobin electrophoresis or an HPLC and a quantitative analysis of hemoglobin fractions (HbA, HbA₂ and HbF) as well as coloring Heinz bodies in a blood smear.

The phenotypic exploration must be followed by genetic analysis. The detection of heterozygotes, asymptomatic in most cases, allowed to identify couples at risk and eventually to propose genetic counseling. In Tunisia, the first step of genetic counseling for hemoglobinopathies was started in 1986 (Chibani et al, 1986). Given the limited resources of treatment of severe hemoglobinopathies, efforts have focused on a community prevention program based on genetic counseling because the socioeconomic conditions of the high risk population, the consanguinity and the reduced infant mortality may increase the number of affected subjects.

Several affected children with abnormal hemoglobin can die before reaching the 10th year of life if the disease is not diagnosed or if the limited economic resources do not permit to take in charge correctly the numerous patients already identified. Heterozygote detection should be conducted in regions with local concentration of the disease and relatively high degree of consanguinity which was estimated to 20,1 % in 2006 (Kerkeni et al, 2006).

Iron deficiency is a major problem for the diagnosis of heterozygous beta-thalassemia since it may mask an elevation of HbA₂ level. The experience in Tunisia demonstrates that premarital screening is the best option and should be mandatory in any prevention program for hemoglobinopathies (Fattoum 2009). Thus, most at risk couples are identified early in the first pregnancy and would regularly produce healthy offspring. Unfortunately many at risk couples yet discover their risk only after the birth of their first affected child. In Tunisia, neonatal screening was decided to reach the maximum of concerned families; its efficiency is more evident in population of at risk regions (Fattoum 2009). Success will depend on a good coordination and a good cooperation between parents and medical staff.

To improve the situation, public education about thalassemias and sickle cell disease is of a great importance and should be carried out through periodic meetings addressed to health professionals including doctors and nurses working in the community, and family members. Also, all means of mass media are helpful as well as the sensitization through patient parents' associations that facilitates the contact with families and the diffusion of information through didactic supports.

Prevention program at national level remains the best alternative to control hemoglobinopathies. It should include: (i) Active sensitization of population, notably among the youth; (ii) Integration of hemoglobin study as a mandatory pre-marital test (iii) Extend the neonatal screening of hemoglobinopathies to all at risk regions; (iv) Maintain updated the national patients register for hemoglobinopathies in the country for prospective prevention actions; (v) Provide freely genetic counseling to carriers and at risk couples for hemoglobinopathies; (Fattoum 2009).

Each heterozygous diagnosed should benefit from a basic information on the genetic and clinical consequences of the consanguinity and the genetic counseling should be based on reliable diagnostic data. Many problems still exist in this area. The difficulties come from the inability to prospectively describe the severity of the syndrome which could affect the child of a given pair. It is difficult to describe objectively the disease because of the variety of events and their variability. The advised is often confronted with two extremes: the couples tend to either minimize or dramatize the situation. Cultural difficulties should not be considered an obstacle, but rather elements of the dialogue.

Molecular analysis

After complete family investigation, the phenotype study sometimes needs a genotype exploration to detect the mutation allowing unambiguous diagnosis confirmation. Such an analysis requires a maximum of clinical and biological informations and, if possible, samples of parents and relatives of the index cases. Venous blood was collected for DNA extraction.

In Tunisia, many molecular techniques like Southern blot, dot-blot hybridization, RFLP PCR, ARMS PCR, classic PCR followed by electrophoresis on polyacrylamide gels in non denaturing (SSCP) and denaturing conditions (DGGE) and sequencing are used for the analysis and identification of known and unknown beta-globin gene mutations (Haj Khelil et al, 2010).

Identification of mutations

The molecular investigations on thalasseмии contributed to establishing the spectrum of mutations in Tunisia (Haj Khelil et al, 2010). The total number of β -thalassemia mutations identified was 24. The codon 39 (C>T) and IVSI 110 (G>A) mutations are largely predominant (from 54 to 70 % of β -thalassemic mutations). In addition, 12 Hb variants from different origins were described in Tunisia. Concerning α -thalassemia, 12 mutations have been detected. The relatively low number of these mutations could be explained by the underestimation of these defects which cannot be observed in adult life.

The important diversity in the phenotypic expression could be explained by the fact that Tunisian population displays a relatively high level of general genetic diversity that could be due to new mutational events or gene flow due to human migrations, and probably reflects some differences in the historical pattern. In fact, several successive civilizations settled in this region for more or less long periods and probably contributed to the present large variety of genetic disorders. Therefore, Tunisia, by its privileged geographical position and relatively mixed origins of its population (El Moncer et al, 2010), represent an interesting area for the study of Hb disorders. In addition, the relatively high level of consanguinity, particularly in rural areas, increases the probability of these genetic disorders.

Application of the antenatal diagnosis

The fact that genetic technology makes the identification of molecular defects easier improves genetic counseling. The aim of genetic counseling is to help families carrying mutant alleles. It helps the medical staff for the potential screening of individuals at risk and to propose the antenatal diagnosis. The study requires informed and written consent from the patient(s) and family members. First, the investigation of the abnormalities responsible for the pathology is performed, followed by confirmation of the diagnosis and then an appropriate management strategy is proposed.

The methods used in the antenatal period are different depending on whether it is diagnostic or screening. Diagnostic methods are based on samples of amniotic fluid (amniocentesis), fetal cells (choriocentesis), or fetal blood (cordocentesis). Antenatal diagnosis is proposed to couples having already given birth to an affected child, and therefore, at high risk. The assays for antenatal diagnosis for hemoglobinopathies began in 1983 using the association between mutations in the β -globin gene and RFLP haplotypes on the β -globin locus (Beldjord et al, 1983). Today, in Tunisia, the combination of molecular biology techniques, such as ARMS-PCR, RFLP-PCR, DGGE and sequencing, allows prenatal diagnosis in a rapid, reliable and inexpensive way, more particularly in families with an index case (Laradi et al, 2000; Fattoum 2006; Moumni et al, 2007).

Antenatal diagnostic testing raises, however, a number of important ethical issues (Gates 1993), some related to diagnostic testing in general and others related to the special circumstances of pregnancy. These issues are most effectively addressed in the context of a broader understanding of the goals of antenatal diagnosis. The dual obligations to the pregnant woman and to the fetus have an important influence on the goals of testing. Testing seldom leads to treatment beneficial to the fetus, but more often can be beneficial to the pregnant woman, particularly if the information provided enhances her ability to make sound decisions about reproductive matters.

The process of antenatal diagnostic testing can, however, limit a woman's sense of control over the decisions made about her pregnancy. It can also provide an opportunity for third parties to become involved in what are usually considered private matters. It is therefore important that the process of testing include adequate counseling and follow-up and that the patient's confidence be respected. As antenatal diagnostic technology expands, both in terms of patients to be tested and diagnoses to be sought, society will face difficult questions concerning access to testing and the justification for its use.

Molecular anthropology

Molecular anthropology is useful in estimating the contribution of different gene pools to the make-up of present-day populations and it tests hypotheses about origin of mutations and historical population movements. In addition, it has played a significant role in our understanding of gene-environment interactions and in the detection of genes in common and complex diseases.

Anthropologists, interested by genetic relationships analyses of human populations and the study of their evolutionary history, have initially used classic genetic markers such as those of ABO blood groups (Mourant et al, 1976), the PI system of alpha 1 antitrypsin (for review see Denden et al., 2012), HLA loci, Rhesus system (e.g., Sanchez-Mazas and Langaney, 1988; Chaabani et al., 2000; Arnaiz-Villena et al. 2010) and particularly those of immunoglobulin GM system known by its unparalleled ability, of a single system, to differentiate human populations (Chaabani, 2002). These studies have demonstrated that the gene pool is not a simple sum of genes, but is a dynamic system, which is hierarchally organized and which maintains the memory of past events in the history of populations. All genetic information has a historical, anthropological, geographical and statistical context, therefore requires co-operation and collaboration between researchers in different fields.

The advances in molecular technologies particularly during the last three decades have allowed the direct analysis of DNA polymorphisms and the use of these DNA markers in several anthropological studies. In some of these studies, nuclear DNA polymorphisms were analyzed in a large number of loci and in others particular genetic materials such as those of maternal (mtDNA) or paternal (Y chromosome) were analyzed. In fact, results and conclusions provided from analyses of these DNA markers have completed and supported those of classic markers. They have given new insights particularly on the reconstruction of human population structure, histories and evolution.

The potential benefits from the molecular research are vast and valuable including: a better understanding of the genetic and evolutionary factors that influence populations; an understanding of genetic architecture of common and complex diseases and a better understanding of the origin of modern humans (e.g., Chaabani, 2002; 2008). The pattern of genetic variation in modern human populations depends on our demographic history (population migrations, bottlenecks and expansions) as well as gene specific factors such as mutation rates, recombination rates and selection pressure. By examining patterns of genetic polymorphisms, we can infer how past demographic events and selection have shaped variation in the genome.

Origin, spread and evolutionary history of beta globin gene mutations

Beside the common Hemoglobin A (HbA) variant, over 300 structural hemoglobin variants have been identified. But their absence or their presence in low frequencies in some world populations limits their anthropological usefulness. However, some of them as the case of HbE variant typical to the Cambodian population could be served as unique population markers. In addition, the different mutational situations that cause diseases present different particular distributions the analysis of which could give us important anthropological information about the origins and the spread of these mutations.

**** The beta S mutation***

The origin of β S mutation has been widely studied. The last studies involving β -globin cluster restriction enzyme and sequence polymorphism showed a multicentric origin for this mutation. In fact, this mutation occurred independently in four different chromosomal backgrounds in sub-Saharan Africa (Benin, Bantu, Senegal, Cameroon) (Pagnier et al, 1984; Lapoumeroulie et al, 1992) and in Asia (Saudi Arabian-Indian) (Kulozik et al, 1986).

All the molecular studies (RFLP, dot-blot and SNP) analyses conducted on the Tunisian sickle patients showed that β S alleles are associated with the Benin haplotype with the description of one or two atypical haplotype(s) in each study (Frikha et al, 1998; Abbas et al, 1991; Haj Khelil et al, 2004; Moumni et al, 2011). In Algeria, this mutation also appears to have a single Benin origin (Pagnier et al, 1984), as in Morocco and in Egypt, confirming a common genetic background for all the North African β S alleles (Haj Khelil et al, 2010). This agrees with a more general conclusion deduced from the analysis of classic markers (Coudray et al, 2006) and DNA markers (El Moncer et al, 2010), which show a general genetic background between North Africans. Evidence suggests that during the Stone Age, the carriers of this allele traveled from Central West Africa across the then-fertile Sahara to the North (Figure 1). This ancient sub-Saharan gene flow is also suggested by the analysis of many classic and DNA markers (e.g., Chaabani et al., 1986; El Moncer et al 2010).

The presence of malaria among agricultural settlements in North Africa favored the HbS gene (Wiesenfeld 1967). Later, as the Sahara began to dry up, there was a surge of migration away from the desert in all directions, spreading the gene further (Bloom, 1995). However, all approaches used to estimate the age of the β S mutation suggest that it arose about 3,000 years ago (Currat et al, 2002). Until now, there has been no evidence of a more ancient presence of this mutation. Its introduction in North Africa is probably more recent and due to the forced migrations from sub-Saharan Africa through the slavery roads and/or to the continuous influx of sub-Saharan Africans through the caravan routes (Bennani et al, 1994).

** The beta thalassemia mutations*

For β -thalassemia mutations, investigations have been conducted to support the hypotheses on the origin and spread of the most frequent one in Tunisia (codon 39 and IVSI 110). The results were compared with those from other countries in the Mediterranean Basin in relation to the geographical, anthropological and historical background of this region.

The analysis of RFLP and sequence haplotypes (SNP and microsatellite) could support the hypothesis of a local origin of the codon 39 mutation in North Africa (Haj Khelil et al, 2010). Indeed, this mutation is predominant in Tunisia, Algeria and Morocco. It is much more common in the western part than in the eastern part of the Mediterranean Basin. Moreover, it shows high haplotype diversity: four RFLP haplotypes and four SNP haplotypes are associated with this mutation in Algeria. The same level of diversity has been observed in Tunisia for both RFLP and SNP haplotypes (Table 1). Codon 39 is likely to have an occidental and ancient origin (chromosomes are recombined in one-third of the cases). It could have been introduced into the Maghreb during the Roman period through Italy and Spain (Henderson et al, 2009). The Roman Empire covered a large part of the Mediterranean area until the 5th century BC when the Byzantine reconquest occurred.

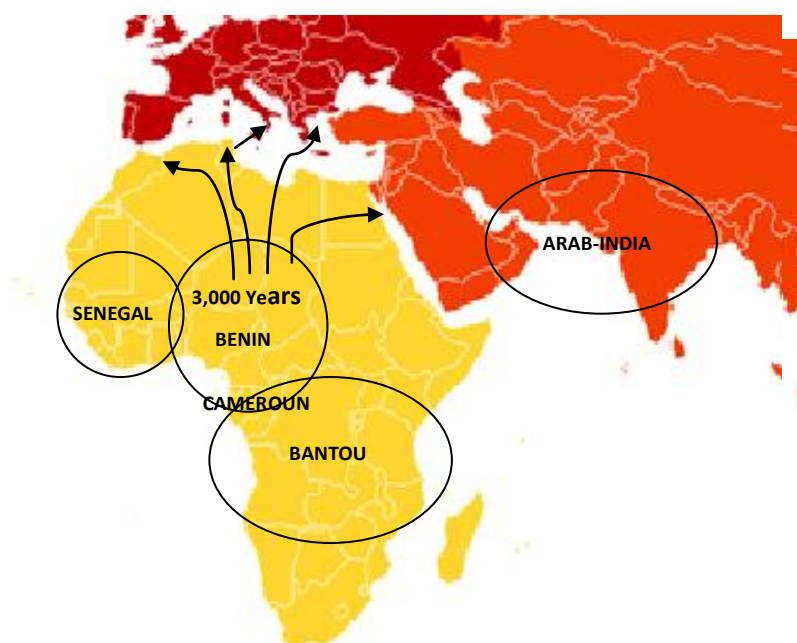


Figure 1:
Distribution of beta S gene and its five associated haplotypes. Arrows show the migration of Benin haplotype over time.

For the IVSI 110 mutation, the comparison of the data in Mediterranean countries strengthens the hypothesis previously proposed as a unique occurrence in the Eastern Mediterranean Basin (Anatolia) during the Neolithic period. Turkey showed the highest haplotype diversity for this mutation associated to six SNP haplotypes (Haj Khelil et al, 2010). Moreover, contrary to the codon 39 mutation, the IVSI 110 is more common in the eastern Mediterranean region (Cyprus, Lebanon, Greece and Turkey). This mutation could have been introduced into North Africa (Tunisia and Algeria) during the Ottoman rule in the 17th century. The fact that this mutation is, in North Africa, the most frequent in Algeria, the second in Tunisia and the seventh in Morocco (infrequent), confirms this hypothesis. Indeed, the Ottoman occupation did not reach Morocco. Its limited introduction in this country would be the result of sporadic Algerian migrations. The results of haplotype analyses argue in favor of this hypothesis. Indeed, a single RFLP haplotype (I) was found in Tunisia; two haplotypes (I and II) were found in Algeria (Table 1). These two haplotypes are the most frequent of the four haplotypes found in Turkey (I, II, IV and IX) (Tadmouri et al, 2001). These findings were confirmed by SNP and microsatellite haplotype analysis in Algeria and in Tunisia showing the association of the IVSI 110 mutation with the same haplotypes: HT1 and HT2. HT1 is by far the most frequent one among six as found previously in Turkey (Table 1). The strong linkage disequilibrium between this haplotype and the IVSI 110 mutation observed in Turkey, Algeria, and Tunisia strengthens the hypothesis of an East Mediterranean origin (ottoman importation) of this mutation in Tunisia and Algeria.

Table 1: RFLP and SNP haplotypes associated with codon 39 and IVSI 110 mutations in Algeria, Tunisia and Turkey (adapted from Haj Khelil et al, 2010).

	Algeria		Tunisia		Turkey	
	RFLP	SNP	RFLP	SNP	RFLP	SNP
Codon 39	I	HTR	I	HT1	II	HT1
	II	HT1	II	HTR	IV	HTR
	*	HT10	A	HTI		
	IX	HT11	5a Nc Nd	HTH		
IVSI 110	I	HT1	I	HT1	I	HT1
	II	HT2		HT2	II	HTR
					IX	HT3
					IV	HT4
						HT5
					HT7	

Both of the genetic markers favor a unicentric origin of the mutation and a probable fixation in the Anatolian area 10,000-9,000 years ago. During that time, that is the end of the pre-pottery Neolithic B and the beginning of the ceramic Neolithic, the populations adopted a production economy. β -thalassaemia conferring a protection towards malaria, hence they would be under positive selection in those areas.

Even if mild forms of malaria may have existed in humans throughout their evolutionary history, genomic data suggest that the most severe form of malaria (*P. falciparum*) did not become endemic until the past 10,000 years in response to climatic and cultural changes. The Neolithic period allowed settlements and the sustenance of high population densities. Indeed, the *P. falciparum* depends to a great extent on the environment and the development of the *Anopheles* mosquito, its vector. Palaeoenvironmental data suggest that a number of Anatolian and Levantine Neolithic sites were probably soft, marshy and could have been malaria-infested, even if no ancient traces of *Plasmodium* or *Anopheles* have been described (Le Mort et al, 2001). On the other hand, palaeopathology reinforces the possible existence of hereditary hemoglobinopathies.

A survey of the Near eastern Epipalaeolithic and Pre-Pottery Neolithic sites (XIIth-VIIth mil. Cal. B.C.) yielded human skeletal remains with bone pathologies including porotic hyperostosis which is a consequence of one of the thalassemiias or sickle cell disease (Lawrence Angel 1966), *cribra orbitalia*, clavaria thickening, osteitic lesions of long bones (Le Mort et al, 2006). Unfortunately, such skeletal manifestations could be possibly due to iron deficiency, rickets or infectious diseases. The combination of the frequency of bone changes together with a high significant mortality might constitute a better indication of a possible hereditary anemia. To confirm this hypothesis, we need a confrontation of genetic, palaeoanthropology, palaeopathology, palaeoenvironment and palaeoclimate. These interdisciplinary fields allow us a better understanding of the emergence and evolution of genetic and parasitic diseases on modern humans.

Conclusion

This study provides an anthropological approach in the analysis of alfa and beta thalassems and Hb variants in Tunisia. Molecular analyses of the β -globin gene allowed the identification of numerous β -thalassemia mutations which help the improvement of treatment, genetic counseling and antenatal diagnosis. Many polymorphisms were found to be associated with the most frequent beta-globin gene mutations in Tunisia, codon 39 and IVSI 110, and permitted to propose the origin and spread of these mutations: a North African origin for codon 39 and an east-Mediterranean origin (Anatolia) for IVSI 110 during the Neolithic period. For the β S mutation of the sickle cell anemia, the β -globin cluster restriction enzyme and sequence polymorphism analyses showed a multicentric origin for this mutation. Arose about 3,000 years ago, this mutation was very likely introduced in North Africa from sub-Saharan Africa. Additional interdisciplinary efforts between geneticists, anthropologists, paleontologists and environmentalists would provide possible new insights on the anthropological history of these diseases.

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