Frontiers in Bioscience
Scholar

Original Research

Genotyping the *BCL11A* Single Nucleotide Polymorphism and Associated Levels of Fetal Hemoglobin in Mauritanian Sickle Cell Patients

Aminetou Taleb Brahim[1,2], Mariem Taleb[2], Harouna Soumaré[3],
Sidi Mohamed Ghaber[2,4], Aminetou Mohamed[1,2,*],
Ali Ould Mohamed Salem Boukhary[1,*]

[1]Unité de Recherche Génomes et Milieux, Faculté des Sciences et Techniques, Université de Nouakchott, Nouveau Campus Universitaire, BP 5026, Nouakchott, Mauritanie
[2]Department of Molecular Research, Maurilab Medical Analysis and Research Institute, 2434 Nouakchott, Mauritania
[3]The African Centre of Excellence for Genomics of Infectious Diseases, Redeemer's University, 232101 Ede, Nigeria
[4]Faculté de Médecine, de Pharmacie et d'Odonto-stomatologie, Université de Nouakchott, Nouveau Campus Universitaire, BP 880 Nouakchott, Mauritanie
*Correspondence: aminetouabbe@yahoo.fr (Aminetou Mohamed); alimedsalem@gmail.com (Ali Ould Mohamed Salem Boukhary)
Academic Editor: George Garinis
Submitted: 27 February 2024   Revised: 18 April 2024   Accepted: 17 May 2024   Published: 12 June 2024

Abstract

Background: Sickle cell disease (SCD) is a major heritable genetic disease in sub-Saharan Africa, including Mauritania. Fetal hemoglobin (HbF) can affect the pathophysiology, moderate the clinical course, and offer prospects for curative treatment of SCD. This study aimed to investigate the influence of single nucleotide polymorphisms (SNPs) in the *BCL11A* gene on the levels of HbF and hematological parameters in Mauritanian sickle cell (*HbSS*) patients. **Methods**: Complete blood count was assessed in 565 patients suspected to have SCD. Polymerase chain reaction (PCR)–restriction fragment length polymorphism was performed to identify the *HbSS*, and sequencing was used for genotyping three SNPs: *rs4671393* (*A>G*) and *rs11886868* (*C>T*) in the intron 2 and *rs1052520* (*G>A*) in the *3′UTR* regions of the *BCL11A* gene in 50 sickle cell patients. **Results**: The prevalence of HbSS among the study population was 8.8% (50/565), and the mean (± standard deviation) of HbF level was 15.0% (± 6.0%). Sequencing showed the presence of three genotypes: AA (13.6%), AG (46.6%), GG (39.6%) in rs4671393; CC (17.6%), CT (48.7%), and TT (33.6%) in *rs11886868*. All samples from HbSS individuals displayed a wild-type genotype in the rs1052520 allele. The prevalence of minor alleles *A* (*rs4671393*) and *C* (*rs11886868*) were 37% and 39%, respectively. There was a statistically significant association ($p = 0.034$) between rs4671393 SNP and elevated HbF (mean 12.72 ± 6.26%). **Conclusions**: The study of three SNPs in the *BCL11A* locus in Mauritanian patients with SCD showed a significant association of *rs4671393* allele with the HbF level. Further research is needed to explore additional SNPs in the *BCL11A* locus and investigate other genetic markers reported to modulate HbF levels, such as *HBS1L-MYB* and *Xmn1-HBG2*, to improve the management of this potentially life-threatening condition in Mauritania.

Keywords: sickle cell disease; fetal hemoglobin; *BCL11A* gene; single nucleotide polymorphisms; Mauritania

1. Introduction

Hemoglobinopathies are genetic disorders affecting the structure or production of the protein portion of hemoglobin [1]. About 5% of the global population carries an abnormal hemoglobin variant; 300,000 to 400,000 infants are born with severe hemoglobinopathies worldwide, and 80% of these cases occur in developing countries [2].

Among the most widespread hemoglobinopathies throughout the world, sickle cell disease (SCD) is caused by an autosomal recessive inheritance of a single nucleotide base substitution (*HBB* c.20$T > $A, *HBB* p.Glu6Val) in the sixth codon of the β-*globin* subunit [3]. This mutation results in amino acid substitution Glu6Val, which characterizes abnormal hemoglobin called HbS [4,5]. Hemoglobin SS genotype (*HbSS*) is the most common type of SCD [6].

Homozygous individuals (*HbSS*) are often affected by severe signs and symptoms of SCD characterized by a painful vaso-occlusive crisis, chronic hemolytic anemia, and an increased risk of infections [7].

Although it is caused by a single amino acid substitution, Glu6Val, SCD is characterized by a wide range of clinical manifestations [8,9]. The cause of this clinical heterogeneity still needs to be fully understood. However, a relatively higher production of fetal hemoglobin (HbF) in adulthood and the consequent increased number of erythrocytes with HbF are likely to be the major factors that modulate the disease phenotype observed in SCD patients [9,10]. Therefore, high HbF levels in adults are among the most common factors that can lead to a considerable decrease in disease severity by mitigating polymerization and precipitation of sickle cell hemoglobin in red blood cells [11].

Publisher's Note: IMR Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

HbF synthesis is generally reduced to very low levels, i.e., less than 0.6% of the total hemoglobin in normal adults [12,13]. However, the HbF level is generally elevated in patients with SCD, ranging from 1% to 30% of the total hemoglobin [11]. HbF expression is regulated by elements linked to the β-globin gene cluster (*11p15.5*) and other quantitative trait loci (QTL) of the *HBB* transgenes, one of which is *BCL11A* locus (*B-cell lymphoma/leukemia 11A*) located on chromosome 2 [14]. The *BCL11A* gene encoding a zinc finger transcription factor was shown to function as a repressor of γ-*globin* expression and HbF production in the erythrocytes of adults [11]. Studies have shown that the inactivation of the BCL11A transcription factor is protective against the complications of SCD in transgenic mice with SCD through the induction of high-level pancellular HbF [15].

A follow-up study involving six SCD patients recently validated the *BCLA11* gene as an effective target for HbF induction therapy [16]. Several single nucleotide polymorphisms (SNPs) influencing the HbF level have been described at this QTL in patients with SCD or thalassemia worldwide [15,17]. These QTLs represent 15–30% of the variation in HbF in sickle cell patients of African origin [11]. Subsequent studies on large populations of patients with thalassemia or SCD showed the distribution of several SNPs, which are significantly associated with high expression of HbF in subjects from various geographical origins [12–14].

SCD is a major heritable genetic disease that affects Africa. With a population consisting of 'white Moors' of Arab descent and Black Africans, Mauritania is also of concern. An earlier study conducted on hemoglobinopathies among 700 blood donors in Nouakchott, the capital city of Mauritania, showed that 16.6% of healthy blood donors were carriers (i.e., heterozygous) of abnormal hemoglobin (21.4% of Mauritanians of Black African origin and 4.5% of white Moors) [18]. Sickle cell trait (HbA/S) was the most common hemoglobin disorder (8.7%), followed by hemoglobin C (HbA/C) trait (3%) and β-thalassemia trait (2.5%) [18]. The southern region of Mauritania was identified as an area of high incidence, with a prevalence of hemoglobin disorders reaching 52% in the Senegal river basin bordering Senegal [19]. Despite these findings, SCD has received little attention from health authorities, and little is known about its impact on public health in the Mauritanian population. In particular, the influence of the *BCL11A* gene polymorphism on HbF levels and the clinical severity of the disease have not been studied in Mauritanian patients with SCD.

In the present study, three SNPs, *rs4671393* (*A>G*) and *rs11886868* (*C>T*) in intron 2 and *rs1052520* (*GA*) in the 3′UTR regions of the BCL11A locus, were investigated, and the associated variation in HbF levels was assessed in Mauritanian homozygous sickle cell patients.

2. Materials and Methods

2.1 Study Design and Participants

The study was conducted from June 2020 to December 2022 at the Maurilab Medical Analysis and Research Institute (MMARI) in Nouakchott. A total of 565 unrelated subjects suspected to be affected by hemoglobinopathy and referred to the MMARI by the Mauritanian SCD association were enrolled. The Mauritanian SCD association supports people with sickle cell disorder in improving their overall quality of life, including free diagnostic testing to detect the presence of abnormal hemoglobin in suspected patients with clinical symptoms suggestive of severe anemia or a family history of anemia. The basic sociodemographic information, including age and sex, was obtained from each participant and recorded in a questionnaire.

The associations between the presence of genetic polymorphisms, HbF levels, and hematologic parameters were analyzed in patients with *HbSS* aged at least 3 years and who had not received hydroxyurea treatment and red blood cell transfusions during the last three months before inclusion.

2.2 Blood Collection, Blood Counts, and Screening of Hemoglobin

Venous blood samples were collected from each patient in K2-ethylenediaminetetraacetic acid (K2-EDTA) tubes (BD Vacutainer, Franklin Lakes, NJ, USA) and immediately analyzed. A complete blood count was obtained by a CELL-DYN Ruby automated Hematology analyzer (Abbott Laboratories, Diagnostics Division, Santa Clara, CA, USA). The blood parameters that were assessed included red blood cell count (RBC), hemoglobin concentration (Hb), sickle hemoglobin (HbS), mean cell (corpuscular) volume (MCV), mean cell hemoglobin concentration (MCHC), fetal hemoglobin (HbF), and hemoglobin A2 (HbA2). Capilarys™ 2 Flex piercing systems (Sebia electrophoresis, Lisses, France) were used to screen for hemoglobin fractions.

2.3 Genotyping Analysis

Only patients with homozygous sickle cell disease (*HbSS*) were included in the genotyping analysis of this study. DNA samples were extracted from peripheral blood using a DNeasy blood and tissue kit (Qiagen, Redwood, CA, USA), according to the manufacturer's instructions. Exon 1 of the β-*globin* gene was analyzed to determine the presence of β^S mutations associated with HbS. Polymerase chain reaction (PCR) was performed to amplify a 739 bp fragment of exon 1 in the β-*globin* gene containing the β^S mutation in a mixture comprising 50 µM of each oligonucleotide primer (PCO6: ATCATTCGTCTGTTTC-CCATT and China I: GTACGGCTGTCATCACTTAGAC-CTCA) [20], 100 ng of genomic DNA, 1× PCR reaction buffer (Qiagen, Valencia, CA, USA), 3.5 mM MgCl$_2$, 125 mM dNTP, and Taq DNA polymerase (0.2 U/µL), us-

Table 1. The primers that were used to detect single nucleotide polymorphisms in the *BCL11A* gene.

SNP	Localization	Primer code	Primer sequence 5′→3′	PCR fragment size
rs4671393	Intron 2	IVS-II-B_2F	CCAGGGAGCCCTCATTTTGT	752 bp
		IVS-II-B_2R	CCCATGGGGCTTCACTTTCT	
rs11886868	Intron 2	IVS-II-B_1F	TGCGCTTCTCAGACCCAAAT	830 bp
		IVS-II-B_1R	GGCTCCCTGGACTCAAACTC	
rs1052520	3′UTR	3′UTRB_1F	CACAGGCAGAGTCAAGTGCT	621 bp
		3′UTR-B_1R	GGGCTGTTTTGCCCAAAGTT	

SNP, single nucleotide polymorphism; F, forward primer; R, reverse primer; PCR, polymerase chain reaction.

ing a Mastercycler nexus (Eppendorf, Issy-les-Moulineaux, France). The PCR product was incubated overnight with DdeI restriction enzyme (New England Biolabs, Hitchin, UK) as previously described [21].

To genotype the SNPs in the *BCL11A* locus associated with HbF levels in homozygous sickle cell patients, three regions containing the SNPs specific to the *BCL11A* gene (*rs11886868*, *rs4671393*, and *rs105252*) were amplified using the primer pairs shown in Table 1. PCR amplification was carried out at a final volume of 25 µL containing 0.04 U Taq DNA polymerase (Qiagen, Chatsworth, CA, USA), 1× PCR reaction buffer (Qiagen, Chatsworth, CA, USA), 0.16 µM of the forward and reverse primers, 0.25 mM deoxynucleoside triphosphate mixture (dGTP, dATP, dTTP, and dCTP), 1.75 mM $MgCl_2$, and 100–200 ng of genomic DNA. PCR was performed using a thermal cycler (Mastercycler nexus) programmed as follows: 94 °C for 10 min, followed by 35 cycles of denaturation at 94 °C for 35 s, annealing at 59 °C for 45 s, and extension at 72 °C for 60 s. This was followed by a final extension at 72 °C for 7 min. The PCR products were sent to the Pasteur Institute in Tunis, Tunisia, for Sanger sequencing. Sequence analysis was performed using Chromas software 2.6 (Informer Technologies Inc., Foster City, CA, USA).

2.4 Data Analysis

The Pandas (https://pandas.pydata.org/), Scipy (https://scipy.org/), and statsmodels packages (https://www.statsmodels.org/stable/index.html) of Python software version 3 (https://www.python.org) were used to conduct statistical analysis. The relationship between HbF levels and hematological parameters was carried out using the Mann–Whitney U test, and the association between HbF levels and genotypes was established using both the Mann–Whitney U test and linear regression.

In the Mann–Whitney U test analysis, three different cut-off values were investigated: 10%, 15%, and 20%. However, 15% was retained since the results of this cut-off for HbF level were quite similar to those obtained from linear regression, which employed the continuous version of HbF as a dependent variable. Before building a linear regression model for genotypes as independent variables, dummy variables were used to convert genotype val-

Table 2. Association between hematological parameters and HbF level in Mauritania sickle cell patients (*HbSS*).

Parameters	HbF <15%		HbF >15%		*p*-value
	Mean	± SD	Mean	± SD	
Age (year)	13.85	10.51	19.6	14.11	0.26
RBC ($\times 10^{12}$/L)	2.75	0.96	3.11	0.67	0.19
Hb (g/dL)	7.39	2.91	8.69	1.32	0.02*
MCV (fL)	87.1	14.1	85.92	10.35	0.98
MCHC (g/dL)	31.1	2	32.35	2.5	0.14
HbF (%)	8.51	3.82	21.06	3.15	<0.0001*
HbS (%)	88.12	3.75	76.3	2.98	<0.0001*
HbA2 (%)	3.3	0.59	2.64	0.51	0.0001*

MCV, mean cellular (corpuscular) volume; Hb, hemoglobin; HbF, fetal hemoglobin; HbA2, hemoglobin A2; HbS, sickle hemoglobin; RBC, red blood cell; MCHC, mean cellular hemoglobin concentration; SD, standard deviation. *Statistically significant.

ues into binary variables. To avoid perfect collinearity, we omitted one dummy variable per genotype (e.g., AA/AG in s4671393). Allelic and genotype frequencies were calculated and tested for Hardy–Weinberg equilibrium (HWE) using Pearson's chi-square test. Statistical significance was set at $p < 0.05$.

3. Results

3.1 Characteristics of the Enrolled Participants

Five hundred and sixty-five participants were enrolled in the study. The participants consisted of 51.3% (290/565) females and 48.7% (275/565) males, with a ratio of 0.95. Most participants (n = 382; 67.6%) had the normal *HbAA*. Further, HbS variants were identified in 112 individuals: heterozygous *HbAS* (10.9%, n = 62) and homozygous *HbSS* (8.8%, n = 50). Seventy-one individuals (12.2%) were characterized as being affected by other hemoglobinopathies, including 23 (4.1%) with *minor β-thalassemia*, 11 (1.9%) with *HbAC*, 14 (2.5%) with hemoglobin *S/β-thalassemia*, 3 (0.5%) with hemoglobin *Hopkins* variant, and 20 (3.5%) with *HbSC* variant (**Supplementary Table 1**).

Table 3. Allelic and genotypic frequencies of SNPs loci *rs4671393* and *rs11886868* in the *BCL11A* gene in Mauritanian sickle cell patients (*HbSS*).

SNP	Genotype	Frequency	Allele	Frequency	χ^2 (HWE)	p-value*
rs4671393	*AA*	0.14	*A*	0.37	4.07	0.065
	AG	0.47	*G*	0.63		
	GG	0.39				
rs11886868	*CC*	0.17	*C*	0.39	11.35	0.001
	CT	0.49	*T*	0.61		
	TT	0.34				

All 50 samples from *HbSS* individuals displayed a wild-type genotype in the *rs1052520* allele. SNP, single nucleotide polymorphism; HWE, Hardy–Weinberg equilibrium. *Significant at $p < 0.05$.

Table 4. Correlation between HbF level and *rs46713983* and *rs11886868* in the *BCL11A* gene in Mauritanian sickle cell patients (*HbSS*).

Locus/chromosome location	SNP	Genotype	N	HbF (%) Mean	$\pm$ SD	Median	p-value
BCL11A/Chr2	*rs4671393 A>G*	*AA+AG*	27	12.72	6.26	12.1	0.034*
		GG	23	9.03	5.77	7.5	
	rs11886868 C>T	*CC+CT*	26	11.83	6.42	10.25	0.25
		TT	21	10.01	6.41	8.9	

Chr2, chromosome 2; SNP, single nucleotide polymorphism. *Statistically significant.

3.2 Relationship between HbF Level and Hematological Parameters

Based on the mean values, the analysis of the hematological parameters of the *HbSS* patients showed normocytic anemia with a low mean ($\pm$ standard deviation, SD) Hb level (7.65 ± 2.71 g/dL) and mean cellular (corpuscular) volume (MCV) (86.86 ± 13.39 fL) within the normal range. Electrophoretic profiles showed a high level of average HbF (15.0 ± 6.0) in these subjects (Table 2). Based on the 15% cut-off level of HbF, 54% (27/50) of patients had an HbF level between 4 and 15% and were classified as "low HbF", while 46% (23/50) had an HbF level ranging from 15 to 26% and were classified as "high HbF". When comparing hematological parameters between these two subgroups, we observed a statistically significant increase ($p = 0.02$) in the hemoglobin concentration in the "high HbF" group (8.7 ± 1.3 g/dL) compared to the "low HbF" group (7.4 ± 2.9 g/dL). Regarding the other hematological parameters, we observed no significant differences between the two HbF groups (Table 2).

3.3 SNPs Detection

Blood samples from the 50 individuals with the *HbSS* genotype were further genotyped for molecular analysis. The sequencing results of the *rs4671393* (*A>G*) and *rs11886868* (*C>T*) alleles in intron 2 of the *BCL11A* gene each showed the presence of three genotypes: *AA* (13.6%), *AG* (46.6%), and *GG* (39.6%) and *CC* (17.6%), *CT* (48.7%), and *TT* (33.6%), respectively (Table 3). Genotyping of the *BCL11A* gene 3′UTR region, where the SNP *rs1052520* is located, in SCD patients showed the presence of only the homozygous wild genotype (*GG*).

The distribution of genotypic and allelic frequencies did not deviate from the HWE ($p > 0.05$) at the *rs4671393* locus, while there was a statistically significant deviation ($p < 0.05$) at the *rs11886868* locus.

Furthermore, relatively high frequencies of minor alleles *A* (0.37) and *C* (0.39) for *rs4671393* and *rs11886868,* respectively, were observed among SCD patients.

Statistical analysis showed a significant correlation between *rs4671393* and the level of HbF (Mann–Whitney test, $p = 0.034$) (Table 4). The presence of the minor allele *A* in *rs4671393* was associated with an elevated level of HbF (mean 12.72 ± 6.26%). Conversely, a statistically significant association ($p = 0.25$) was not observed between the *rs11886868* minor allele and HbF level (11.83 ± 6.42%) (Table 4). Similar results were obtained using linear regression analysis (**Supplementary Table 2**).

4. Discussion

In SCD, a single β6 Glu–Val amino acid substitution leads to potentially life-threatening complications. Some patients tolerate the disease and survive for years or even decades without any notable vascular pathology, while others may present severe and fatal clinical signs [21–23]. This highlights the importance of studying the polymorphisms

contributing to the observed clinical heterogeneity [23,24]. In the present study, the prevalence of *HbSS* among the highly selected participants was 8.8%. Deyde *et al.* [18] reported that 8.7% of Mauritanian healthy blood donors were carriers of the sickle cell trait (*HbAS*), but none had sickle cell disease (*HbSS*), as expected in healthy populations. Veten *et al.* [25] reported a slightly lower frequency (5.71%; 60/1050) of sickle cell mutation (*HbS*) carries among another group of blood donors, including 5 (8.3%) individuals homozygous (*HbSS*) for the mutant allele. Various hematological and biochemical parameters determined the phenotypic characterization of sickle cell in 50 HbSS study participants. Our results showed normocytic anemia in these 50 individuals with *HbSS*. These results agree with previously published data [26]. Furthermore, a high average HbF level (15.0 ± 6.0%) was observed among the study participants despite excluding those under three years of age. This rate is higher than those reported in other studies carried out in children with sickle cell disease in Nigeria, Uganda, and other sub-Saharan African countries where mean ($\pm$ SD) HbF values of 9.9 ± 6.0%, 9.0 ± 5.6%, and 8.9 ± 6.4% were reported, respectively [11,27,28].

HbF is known as the principal SCD genetic modifier, and the presence of ≥ 15% HbF in the whole blood of an SCD patient was reported to reduce the clinical severity of the disease. Earlier studies have shown that a 20% HbF level in the whole blood is associated with an amelioration of sickle cell disease symptoms, although a linear trend was not found between HbF levels and morbidity [29,30]. Several factors, including age, genetics, and environment, could explain this variation. In addition, a significant association was observed between HbF and hemoglobin levels in our study. Our findings were similar to those of Chaouch *et al.* [30], suggesting the important role of HbF in the modulation of anemia in sickle cell patients.

This is the first study focusing on the genotyping of three SNPs (*rs118868686*, *rs4671393*, and *rs1052520*) in the *BCL11A* gene and their correlation with HbF levels in Mauritanian subjects with SCD. In a previous study that genotyped 95 SNPs, including 17 at the *BCL11A* locus, in 1032 African–Americans with sickle cell anemia, Galarneau *et al.* [31] found that *rs4671393* was the genetic marker that was most strongly associated with HbF levels. In that study, they also found two other SNPs in intron 2 of *BCL11A*, *rs7599488* and *rs10189857*, which were associated with HbF levels. In the present study, these latter SNPs were not included in our molecular analysis.

Our results showed the presence of three different genotypes for *rs4671393* and *rs11886868*, with a slightly higher prevalence of minor alleles than those reported in Cameroonians [32]. This slight difference can be explained by the ethnic diversity of our study population, which includes a high proportion of non-Black African populations and the relatively small number of SCD patients included and analyzed. Regarding *rs1052520*, a single homozygous genotype (*GG*) was observed in all individuals with *HbSS* (n = 50), which suggests that this SNP may be fixed and may, therefore, not be suitable as a genetic marker in Mauritania.

In 2007, Menzel *et al.* [13] reported that intron 2 of the *BCL11A* gene has the strongest associations with HbF variation in a 14 kb sequence. In addition, genome-wide association studies identified the *rs4671393* SNP as the determinant marker of the HbF level [32]. This SNP alone explained 10% of the variation in HbF levels in patients with sickle cell anemia from northern Brazil [33]. In addition, the minor A allele was also associated with significantly higher HbF levels [32]. It is worth noting that our results revealed a statistically significant correlation between rs4671393 and HbF level in individuals with HbSS. Indeed, the presence of the minor (*A*) allele was associated with the HbF level increase in our study population. These results are similar to those found in an Angolan pediatric population [34].

The main limitations of the present study are the inclusion of a small number of individuals with SCD and a limited number of SNPs analyzed in the *BCL11A* locus or reported to modulate HbF levels.

5. Conclusions

The results of the present study highlight the differential frequencies of three SNPs in the BCL11A locus in Mauritanian individuals with HbSS that were previously reported to be associated with HbF levels. The HbF level is crucial in determining the severity of SCD, and genetic modification of HbF expression may offer clinical benefits in diagnosis and disease monitoring. The findings of the present study have important implications for genetic counseling and clinical management of SCD patients.

However, further research is needed to explore the association between genetic markers and HbF levels to improve the characterization of sickle cell disease and potentially improve the management of this life-threatening condition.

Availability of Data and Materials

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials.

Author Contributions

ATB collected data, performed blood and molecular analyses, interpreted the data, wrote the first draft of the manuscript. MT collected data and performed blood analysis. HS performed statistical analysis. SMG performed statistical analysis, interpreted data and supervised laboratory analyses. AM and AOMSB conceived, designed, and supervised the research, wrote, critically reviewed and edited the manuscript. All authors have participated sufficiently in

the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity. All authors read and approved the final manuscript. All authors contributed to editorial changes in the manuscript.

Ethics Approval and Consent to Participate

Acknowledgment

Funding

Conflict of Interest

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.31083/j.fbs1602011.

References

[1] Couque N, Trawinski E, Elion J. Génétique des maladies de l'hémoglobine. Revue Francophone des Laboratoires. 2016; 481: 49–60. (In French)

[2] Warghade S, Britto J, Haryan R, Dalvi T, Bendre R, Chheda P, et al. Prevalence of hemoglobin variants and hemoglobinopathies using cation-exchange high-performance liquid chromatography in central reference laboratory of India: A report of 65779 cases. Journal of Laboratory Physicians. 2018; 10: 73–79.

[3] Geye T, Ndour EHM, Ly ID, Diallo RN, Geuye PM, Diop PA, et al. Prévalence de l'alphathalassémie au sein d'une population drépanocytaire sénégalaise. Rev. Cames Sante. 2017; 5: 95–101. (In French)

[4] Mattioni S, Stojanovica K, Girota R, Lionneta F. La drépanocytose en France. Revue francophone des laboratoires-avril. 2016; 481: 61–66.

[5] Renaudier P. Sickle cell pathophysiology. Transfusion Clinique et Biologique. 2014; 21: 178–181. (In French)

[6] Abdullahi SU, DeBaun MR, Jordan LC, Rodeghier M, Galadanci NA. Stroke Recurrence in Nigerian Children With Sickle Cell Disease: Evidence for a Secondary Stroke Prevention Trial. Pediatric Neurology. 2019; 95: 73–78.

[7] Bachir D. La drépanocytose. Revue Française des Laboratoires. 2000; 324: 29–35. (In French)

[8] Adeyemo TA, Ojewunmi OO, Oyetunji IA, Rooks H, Rees DC, Akinsulie AO, et al. A survey of genetic fetal-haemoglobin modifiers in Nigerian patients with sickle cell anaemia. PLoS ONE. 2018; 13: e0197927.

[9] Lettre G, Sankaran VG, Bezerra MAC, Araújo AS, Uda M, Sanna S, et al. DNA polymorphisms at the BCL11A, HBS1L-MYB, and beta-globin loci associate with fetal hemoglobin levels and pain crises in sickle cell disease. Proceedings of the National Academy of Sciences of the United States of America. 2008; 105: 11869–11874.

[10] Steinberg MH. Fetal hemoglobin in sickle cell anemia. Blood. 2020; 136: 2392–2400.

[11] Nicolau M, Vargas S, Silva M, Coelho A, Ferreira E, Mendonça J, et al. Genetic modulators of fetal hemoglobin expression and ischemic stroke occurrence in African descendant children with sickle cell anemia. Annals of Hematology. 2019; 98: 2673–2681.

[12] Rochette J, Craig JE, Thein SL. Fetal hemoglobin levels in adults. Blood Reviews. 1994; 8: 213–224.

[13] Menzel S, Garner C, Gut I, Matsuda F, Yamaguchi M, Heath S, et al. A QTL influencing F cell production maps to a gene encoding a zinc-finger protein on chromosome 2p15. Nature Genetics. 2007; 39: 1197–1199.

[14] Ngo D, Bae H, Steinberg MH, Sebastiani P, Solovieff N, Baldwin CT, et al. Fetal hemoglobin in sickle cell anemia: genetic studies of the Arab-Indian haplotype. Blood Cells, Molecules & Diseases. 2013; 51: 22–26.

[15] Steinberg MH, Chui DHK, Dover GJ, Sebastiani P, Alsultan A. Fetal hemoglobin in sickle cell anemia: a glass half full? Blood. 2014; 123: 481–485.

[16] Esrick EB, Lehmann LE, Biffi A, Achebe M, Brendel C, Ciuculescu MF, et al. Post-Transcriptional Genetic Silencing of BCL11A to Treat Sickle Cell Disease. The New England Journal of Medicine. 2021; 384: 205–215.

[17] Makani J, Menzel S, Nkya S, Cox SE, Drasar E, Soka D, et al. Genetics of fetal hemoglobin in Tanzanian and British patients with sickle cell anemia. Blood. 2011; 117: 1390–1392.

[18] Deyde VM, Lo BB, Khalifa IO, Ly B, Ball A, Fattoum S. Epidemiological profile of hemoglobinopathies in the Mauritanian population. Annals of Hematology. 2002; 81: 320–321.

[19] Mahmoud T, Sahli C, Hadj Fredj S, Amri Y, Othmani R, Mohamed GS, et al. Epidemiological and molecular study of hemoglobinopathies in Mauritanian patients. Molecular Genetics & Genomic Medicine. 2022; 10: e2048.

[20] Abaza H, Gara Y, Ben Chaabene A, Douik H, Harzallah L, Boussen H et al. Variation phénotypique et moléculaire des hémoglobinopathies en milieu carcinologique. Tunisie Medicale. 2013;91: 129–133. (In French)

[21] Chang JC, Kan YW. Antenatal diagnosis of sickle cell anaemia by direct analysis of the sickle mutation. Lancet. 1981; 2: 1127–1129.

[22] Laghdaf Sidi M, N'Diaye AM, Cheikh M, Heinhane MM. Sickle Cell Disease in Mauritania: epidemiological, clinical and therapeutic aspects about 135 cases. La Tunisie Medicale. 2022; 100: 313–322. (In French)

[23] Akinsheye I, Alsultan A, Solovieff N, Ngo D, Baldwin CT, Sebastiani P, et al. Fetal hemoglobin in sickle cell anemia. Blood. 2011; 118: 19–27.

[24] El-Ghamrawy M, Yassa ME, Tousson AMS, El-Hady MA, Mikhaeil E, Mohamed NB, et al. Association between BCL11A, HSB1L-MYB, and XmnI γG-158 (C/T) gene polymorphism and hemoglobin F level in Egyptian sickle cell disease patients. Annals of Hematology. 2020; 99: 2279–2288.

[25] Veten FM, Abdelhamid IO, Meiloud GM, Ghaber SM, Salem ML, Abbes S, et al. Hb S [β6(A3)Glu→Val, GAG>GTG]

and β-globin gene cluster haplotype distribution in Mauritania. Hemoglobin. 2012; 36: 311–315.

[26] Gueye Tall F, Martin C, Ndour EHM, Renoux C, Ly ID, Connes P, *et al*. Combined and differential effects of alpha-thalassemia and HbF-quantitative trait loci in Senegalese hydroxyurea-free children with sickle cell anemia. Pediatric Blood & Cancer. 2019; 66: e27934.

[27] Mpalampa L, Ndugwa CM, Ddungu H, Idro R. Foetal-haemoglobin and disease severity in sickle cell anaemia patients in Kampala, Uganda. BMC Blood Disorders. 2012; 12: 11.

[28] Adeodu OO, Akinlosotu MA, Adegoke SA, Oseni SBA. Foetal Haemoglobin and Disease Severity in Nigerian Children with Sickle Cell Anaemia. Mediterranean Journal of Hematology and Infectious Diseases. 2017; 9: e2017063.

[29] Powars DR, Weiss JN, Chan LS, Schroeder WA. Is there a threshold level of fetal hemoglobin that ameliorates morbidity in sickle cell anemia? Blood. 1984; 63: 921–926.

[30] Chaouch L, Moumni I, Ouragini H, Darragi I, Kalai M, Chaouachi D, *et al*. rs11886868 and rs4671393 of BCL11A associated with HbF level variation and modulate clinical events among sickle cell anemia patients. Hematology. 2016; 21: 425–429.

[31] Galarneau G, Palmer CD, Sankaran VG, Orkin SH, Hirschhorn JN, Lettre G. Fine-mapping at three loci known to affect fetal hemoglobin levels explains additional genetic variation. Nature Genetics. 2010; 42: 1049–1051.

[32] Wonkam A, Mnika K, Ngo Bitoungui VJ, Chetcha Chemegni B, Chimusa ER, Dandara C, *et al*. Clinical and genetic factors are associated with pain and hospitalisation rates in sickle cell anaemia in Cameroon. British Journal of Haematology. 2018; 180: 134–146.

[33] Cardoso GL, Diniz IG, Silva ANLMD, Cunha DA, Silva Junior JSD, Uchôa CTC, *et al*. DNA polymorphisms at BCL11A, HBS1L-MYB and Xmn1-HBG2 site loci associated with fetal hemoglobin levels in sickle cell anemia patients from Northern Brazil. Blood Cells, Molecules & Diseases. 2014; 53: 176–179.

[34] Delgadinho M, Ginete C, Santos B, Miranda A, Brito M. Genotypic Diversity among Angolan Children with Sickle Cell Anemia. International Journal of Environmental Research and Public Health. 2021; 18: 5417.