

RESEARCH ARTICLE

HLA haplotype frequencies and diversity in patients with hemoglobinopathies

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Abstract

The genetic diversity of the human leukocyte antigen (HLA) system was shaped by evolutionary constraints exerted by environmental factors. Analyzing HLA diversity may allow understanding of the underlying pathways and offer useful tools in transplant setting. The aim of this study was to investigate the HLA haplotype diversity in patients with sickle cell disease (SCD, $N = 282$) or β -thalassemia (β -Thal, $N = 60$), who received hematopoietic cell transplantation (HCT) reported to Eurocord and the

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Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC). We identified 405 different HLA-A-B-DRB1 haplotypes in SCD and 108 in β -Thal patients. Using data from African and European populations of the “1000 Genomes Project” for comparison with SCD and β -Thal, respectively, we found that the haplotypes HLA-A*30-B*14-DRB1*15 (OR 7.87, 95% CI: 1.66–37.3, $p_b = 0.035$), HLA-A*23-B*08 (OR 6.59, 95% CI: 1.8–24.13, $p_b = 0.023$), and HLA-B*14-DRB1*15 (OR 10.74, 95% CI: 3.66–31.57, $p_b = 0.000$) were associated with SCD, and the partial haplotypes HLA-A*30-B*13 and HLA-A*68-B*53 were associated with β -Thal (OR 4.810, 95% CI: 1.55–14.91, $p_b = 0.033$, and OR 17.52, 95% CI: 2.81–184.95, $p_b = 0.011$). Our results confirm the extreme HLA genetic diversity in SCD patients likely due to their African ancestry. This diversity seems less accentuated in patients with β -Thal. Our findings emphasize the need to expand inclusion of donors of African descent in HCT donor registries and cord blood banks.

KEYWORDS

haplotypes, hemoglobinopathies, HLA, sickle cell disease, β -thalassemia

1 | INTRODUCTION

Hemoglobinopathies are frequent inherited blood disorders affecting approximately 5% of the population worldwide [1]. Among them, sickle cell disease (SCD) and β -thalassemia (β -Thal) are, in their homozygous expression, life-threatening disorders mainly alleviated by substitutive therapeutic options, such as long-term blood transfusions and/or fetal hemoglobin induction [2, 3]. Structurally characterized either by a glutamic acid to valine amino acid change of the hemoglobin β chain or defective/inefficient synthesis of hemoglobin due to various point mutations, respectively, SCD and β -Thal have long been considered as prototypic monogenic disorders [1]. Further knowledge demonstrated the involvement of other pathways/processes such as immunological underpinnings of the evolution of the two disorders [4]. Until a few years ago, allogeneic hematopoietic cell transplantation (HCT) from human leukocyte antigen (HLA) identical siblings or alternative donors was the only available curative treatment; however, a variety of novel disease-modifying drugs, gene addition and gene editing strategies have been recently developed and are, now, the object of many ongoing clinical studies yielding variable results [2, 5, 6].

Due to its dual implications, both in the development of disease-related complications and in the successful matching of donor-recipient pairs in HCT settings, the HLA system and its genetic diversity constitute one of the best candidates deserving to be studied. Because of the extreme polymorphism of the HLA allelic pool, haplotype-based analyses were developed especially as some of the so-called HLA ancestral haplotypes are endowed by inflammatory properties [7, 8], an important notion given the central role of inflammatory processes in the evolution of the two disorders [4, 9, 10].

Several studies have reported the frequencies of the most frequent HLA haplotypes in France [11, 12] and Europe, mainly from bone marrow donor registry HLA data [13–15], but the haplotype diversity of

ethnic minorities has rarely been studied [16, 17]. To date, few studies explored HLA genotype and haplotype information in patients with hemoglobinopathies explaining difficulties to find potential unrelated donors in international registries [18, 19].

The objective of this study was to investigate the HLA haplotype frequency and diversity, encompassing the HLA-A, HLA-B, and HLA-DRB1 loci, in patients with SCD or β -Thal who received HLA-matched sibling HCT.

2 | METHODS

2.1 | Patient characteristics

Demographic and clinical data of 555 patients with hemoglobinopathy, who underwent a first HLA-identical sibling donor HCT from 2000 to 2019 in 30 centers, were obtained from the Société Francophone de Greffe de Moelle et de Thérapie Cellulaire (SFGM-TC) registry. Additional information was collected directly from transplant centers, by Eurocord, and merged with the SFGM-TC data in a retrospective dataset for analysis.

First field (antigenic) HLA specificities for at least HLA-A, HLA-B, and HLA-DRB1 alleles were available for 342 patients, and HLA data were missing or incomplete for the others. Slightly more than half of the patients were males ($N = 177$, 51.8%). The majority of patients were children ($N = 321$, 94%), and the median age was 8.37 years (range: 0.98–46.02). Patients were transplanted in France (74.6%), Belgium (25.1%), and Switzerland (0.3%). Two-hundred eighty-two patients were transplanted for SCD and 60 for β -Thal. The two population groups were analyzed separately according to their disease and, consequently, anthropogenetic origin (namely, SCD patients were mostly of African origin while β -Thal patients of Mediterranean and Middle Eastern descentance).

The study protocol was approved by Eurocord and SFGM-TC institutional review boards.

2.2 | HLA typing

HLA antigen-level typing data (first field) were used to reconstruct HLA haplotypes and perform analyses.

2.3 | Statistical analysis

Microsoft Excel, SPSS v.28, and R version 3.5.3 (R Project for Statistical Computing) were used for the descriptive statistics including frequencies, percentages, and the median with minimum and maximum ranges. The publicly available Easy-HLA website [20] was used to reconstruct HLA-haplotypes of each patient from two-digit HLA alleles.

The comparisons of HLA haplotypes between SCD and African populations, or β -Thal and European populations from the "1000 Genomes Project" database (<https://www.internationalgenome.org>), were performed using a chi-square test. Odds ratio (OR) and 95% confidence intervals (CI) were calculated to assess the risk conferred by specific HLA haplotypes. Corrections for multiple tests were performed with the Bonferroni method [21, 22]. Findings were considered statistically significant for p -value after Bonferroni correction (p_b) < 0.05. The frequency of SCD and β -Thal patients and their characteristics in the other super populations present in the "1000 Genomes Project" (namely, South Asian, East Asian, and Admixed American) did not justify further comparisons.

3 | RESULTS

3.1 | Sickle cell disease patients

We identified 405 different HLA-A-B-DRB1 haplotypes in 282 SCD patients. Table 1 shows the eight most frequent haplotypes (observed five or more times), among which the HLA-A*34-B*44-DRB1*15 was the most frequent (frequency, $f = 0.0159$). Overall, 55 patients (19.5%) had at least one of these eight most frequent HLA-A-B-DRB1 haplotypes.

When considering the two haplotypes for each patient, the six most frequent HLA-A-B-DRB1 haplotype-based genotypes are shown in Table 2. Only one of these genotypes contains one of the eight most frequent haplotypes.

Analyzing partial haplotypes involving DNA stretch of HLA-A-B and HLA-B-DRB1 regions, Table 3 shows frequencies for the most frequent partial haplotypes, observed 10 or more times. The most frequent partial haplotypes were A*66-B*58 ($f = 0.0248$) and B*14-DRB1*15 ($f = 0.0372$), respectively.

We compared the frequencies of the most recurrent HLA complete and partial SCD haplotypes to those reported in the African part of the "1000 Genomes Project" (Table 4). As expected, we observed a great

TABLE 1 The eight most frequent HLA-A-B-DRB1 haplotypes in sickle cell disease patients ($N_p = 282$).

HLA-A-B-DRB1 haplotype(haplotypes, $N_H = 564$)	N_H	Frequency
A*34~B*44~DRB1*15	9	0.0159
A*30~B*14~DRB1*15	8	0.0142
A*36~B*53~DRB1*11	7	0.0124
A*66~B*58~DRB1*13	7	0.0124
A*66~B*58~DRB1*15	7	0.0124
A*30~B*42~DRB1*03	6	0.0106
A*30~B*57~DRB1*13	6	0.0106
A*68~B*07~DRB1*15	5	0.0089
Total	55	0.0974

Abbreviations: N_H , number of haplotypes; N_p , number of patients.

TABLE 2 The six most frequent HLA-A-B-DRB1 haplotype-based genotypes in sickle cell disease patients ($N_p = 282$).

HLA-A-B-DRB1 haplotype-based genotype	N_H	Frequency
A*01~B*37~DRB1*07 - A*30~B*07~DRB1*13	2	0.007
A*02~B*14~DRB1*15 - A*33~B*53~DRB1*08	2	0.007
A*02~B*40~DRB1*07 - A*80~B*15~DRB1*01	2	0.007
A*23~B*08~DRB1*07 - A*23~B*44~DRB1*15	2	0.007
A*23~B*08~DRB1*07 - A*30~B*57~DRB1*13	2	0.007
A*23~B*08~DRB1*13 - A*33~B*35~DRB1*11	2	0.007
Total	12	0.042

Abbreviations: N_H , number of haplotypes; N_p , number of patients.

similarity between these two populations in terms of HLA haplotype frequencies, however, with some significant differences for the haplotypes A*30-B*14-DRB1*15 (OR 7.87, 95% CI: 1.66–37.3, $p_b = 0.035$), A*23-B*08 (OR 6.59, 95% CI: 1.8–24.13, $p_b = 0.023$), and the B*14-DRB1*15 (OR 10.74, 95% CI: 3.66–31.57, $p_b = 0.000$), which were enriched in patients with SCD.

3.2 | B-thalassemia patients

The analysis of HLA haplotype distribution in β -Thal showed 108 different HLA-A-B-DRB1 haplotypes in 60 patients. The three most frequent were: A*01-B*08-DRB1*03 ($N = 3$; $f = 0.025$), A*24-B*35-DRB1*11 ($N = 3$; $f = 0.025$), and A*30-B*13-DRB1*07 ($N = 3$; $f = 0.025$).

Considering the two haplotypes for each patient, we did not observe any recurrent HLA-A-B-DRB1 haplotype-based genotype. Table 5

TABLE 3 The most frequent partial haplotypes in sickle cell disease patients ($N_H = 564$ haplotypes).

HLA-A-B partial haplotype	N_H	Frequency
A*66~B*58	14	0.0248
A*02~B*45	12	0.0213
A*23~B*15	12	0.0213
A*30~B*42	12	0.0213
A*23~B*07	11	0.0195
A*36~B*53	11	0.0195
A*74~B*15	11	0.0195
A*02~B*53	10	0.0177
A*23~B*08	10	0.0177
A*30~B*14	10	0.0177
A*34~B*44	10	0.0177
Total	123	0.218
HLA-B-DRB1 partial haplotype	N_H	Frequency
B*14~DRB1*15	21	0.0372
B*15~DRB1*11	20	0.0355
B*44~DRB1*15	20	0.0355
B*58~DRB1*13	18	0.0319
B*53~DRB1*11	14	0.0248
B*58~DRB1*15	12	0.0213
B*15~DRB1*13	11	0.0195
B*42~DRB1*03	11	0.0195
B*08~DRB1*13	10	0.0177
B*44~DRB1*13	10	0.0177
Total	147	0.2606

Abbreviation: N_H , number of haplotypes.

shows the frequencies for partial haplotypes observed three or more times ($N = 120$ haplotypes).

The comparison of the frequencies of the most frequent HLA-A-B-DRB1 β -Thal haplotypes with those of the European population of the “1000 Genomes Project” did not show any significant differences. Interestingly, for the HLA-A-B partial haplotypes, the two most frequent ones, A*30-B*13 and A*68-B*53, were more prevalent in β -Thal patients and, therefore, associated with the disease (OR 4.810, 95% CI: 1.55–14.91, $p_b = 0.033$, and OR 17.52, 95% CI: 2.81–184.95, $p_b = 0.011$, respectively) (Table 6). No significant differences in frequencies between β -Thal and European populations were observed within the HLA-B-DRB1 haplotypes.

4 | DISCUSSION

Discovered in the middle of the last century, the HLA system has come back to the limelight during the last decade. The HLA diversity was shaped by environmental pressures, with that exerted by microbes being the leading one [23, 24]. Consequently, the extreme variety of

TABLE 4 HLA haplotypes in SCD patients and their frequencies compared to African population.

Haplotype	SCD population frequency	African population frequency	Adj. p (p_b)	OR [95% CI]	p	HLA-A-B Haplotype	Adj. p (p_b)	OR [95% CI]	p	HLA-B-DRB1 Haplotype	SCD population frequency	African population frequency	Adj. p (p_b)	OR [95% CI]	p
A*34~B*44~DRB1*15	0.0159	0.0104	0.612	5.508	0.0133	A*66~B*58	0.245	2.944	0.0372	B*14~DRB1*15	0.0030	0.0030	0.000	0.000	0.000
A*30~B*14~DRB1*15	0.0142	0.0015	0.004	0.035	0.0213	A*02~B*45	0.236	2.830	0.0355	B*15~DRB1*11	0.0267	0.0267	0.802	8.825	[3.66–31.57]
A*36~B*53~DRB1*11	0.0124	0.0118	0.702	6.317	0.0213	A*23~B*15	0.406	4.873	0.0355	B*44~DRB1*15	0.0296	0.0296	0.887	9.758	
A*66~B*58~DRB1*13	0.0124	0.0037	0.076	0.682	0.0213	A*30~B*42	0.007 ^a	0.085	0.0319	B*58~DRB1*13	0.0200	0.0200	0.399	4.385	
A*66~B*58~DRB1*15	0.0124	0.0059	0.304	2.735	0.0195	A*23~B*07	0.917	11.009	0.0248	B*53~DRB1*11	0.0333	0.0333	0.081	0.888	
A*30~B*42~DRB1*03	0.0106	0.0185	0.077	0.692	0.0195	A*36~B*53	0.727	8.725	0.0213	B*58~DRB1*15	0.0163	0.0163	0.889	9.774	
A*30~B*57~DRB1*13	0.0106	0.0067	0.632	5.684	0.0195	A*74~B*15	0.363	4.358	0.0195	B*15~DRB1*13	0.0252	0.0252	0.159	1.744	
A*68~B*07~DRB1*15	0.0089	0.0037	0.289	2.599	0.0177	A*02~B*53	0.010 ^a	0.120	0.0195	B*42~DRB1*03	0.0333	0.0333	0.018 ^a	0.199	
						A*23~B*08	0.002	0.023	0.0177	B*08~DRB1*13	0.0141	0.0141	0.972	10.688	
						A*30~B*14	0.0037	0.090	0.0177	B*44~DRB1*13	0.0037	0.0037	0.007 ^a	0.082	
						A*34~B*44	0.0118	0.640	7.683						

Abbreviations: HLA, human leukocyte antigen; p_b , corrected p -value; SCD, sickle cell disease.
^aNo significant p_b after Bonferroni correction.

TABLE 5 The most frequent partial haplotypes in β -Thal patients ($N_H = 120$ haplotypes).

HLA-A-B partial haplotype	N_H	Frequency
A*30~B*13	5	0.0417
A*68~B*53	5	0.0417
A*02~B*51	4	0.0333
A*01~B*08	3	0.0250
A*01~B*52	3	0.0250
A*02~B*07	3	0.0250
A*02~B*35	3	0.0250
A*02~B*50	3	0.0250
A*11~B*51	3	0.0250
A*24~B*35	3	0.0250
Total	35	0.2917
HLA-B-DRB1 partial haplotype	N_H	Frequency
B*08~DRB1*03	4	0.0333
B*13~DRB1*07	4	0.0333
B*44~DRB1*04	4	0.0333
B*18~DRB1*03	3	0.0250
B*35~DRB1*11	3	0.0250
B*44~DRB1*01	3	0.0250
B*49~DRB1*13	3	0.0250
B*53~DRB1*01	3	0.0250
Total	27	0.2249

Abbreviation: N_H , number of haplotypes.

the HLA allelic diversity, which can deal with any foreign molecular structure, constitutes a powerful and pivotal element of anti-infectious immune response. The HLA antigen presentation-based properties may, however, yield deleterious effects such as the association with auto-immune/inflammatory conditions and, importantly, constituting the main barrier to a wide use of transplantation-based therapeutic approaches. More than 30,000 alleles reported to date (IMGT HLA database, <https://www.imgt.org/IMGTindex/HLA.php>) hamper association studies and precise matching in HCT settings.

Accordingly, we herein analyzed the HLA haplotype diversity in two population groups transplanted for SCD or β -Thal to explore possible associations with the diseases per se, and to evaluate the likelihood to find unrelated HLA-matched donors for patients with SCD or β -Thal.

As expected, given the African origin of patients with SCD, we observed a great diversity of HLA haplotypes. Among them, eight were frequent, as previously reported in Afro-American populations, in particular the A*30-B*42-DRB1*03 and the A*36-B*53-DRB1*11 haplotypes [25]. The latter has been previously described in both Brazilian and European SCD patients [19]. Similarly, the most frequent two-locus HLA-A-B partial haplotypes in SCD patients have already been described, even if with different frequencies, in Black individuals [26]. Of note, none of the reported haplotypes in this population correspond to the well-known HLA ancestral haplotypes (AH) that

TABLE 6 HLA haplotypes in β -Thal patients and their frequencies compared to European population.

Haplotype HLA-A-B-DRB1	B-Thal population frequency	OR [95% frequency CI]	Adj. p (p_b)	Haplotype HLA-A-B	B-Thal population frequency	OR [95% frequency CI]	Adj. p (p_b)	Haplotype HLA-B-DRB1	B-Thal population frequency	OR [95% frequency CI]	Adj. p (p_b)	European population frequency	OR [95% frequency CI]	Adj. p (p_b)
A*01~B*08~DRB1*03	0.0250	0.0532	0.258	A*30~B*13	0.0417	4.810 [1.55- 14.91]	0.003	B*08~DRB1*03	0.0333	0.0656	0.221	1.989	0.221	1.989
A*24~B*35~DRB1*11	0.0250	0.0037	0.031 ^a	A*68~B*53	0.0417	17.52 [2.81- 184.95]	0.001	B*13~DRB1*07	0.0333	0.0173	0.275	2.475	0.275	2.475
A*30~B*13~DRB1*~07	0.0250	0.0025	0.017 ^a	A*02~B*51	0.0333	0.0297	0.775	B*44~DRB1*04	0.0333	0.0458	0.811	7.299	0.811	7.299
				A*01~B*08	0.0250	0.0705	0.071	B*18~DRB1*03	0.0250	0.0161	0.450	4.050	0.450	4.050
				A*01~B*52	0.0250	0.0012	0.008 ^a	B*35~DRB1*11	0.0250	0.0173	0.473	4.257	0.473	4.257
				A*02~B*07	0.0250	0.0322	1.000	B*44~DRB1*01	0.0250	0.0124	0.230	2.070	0.230	2.070
				A*02~B*35	0.0250	0.0161	0.450	B*49~DRB1*13	0.0250	0.0037	0.031 ^a	0.279	0.031 ^a	0.279
				A*02~B*50	0.0250	0.0074	0.099	B*53~DRB1*01	0.0250	0.0025	0.017 ^a	0.153	0.017 ^a	0.153
				A*11~B*51	0.0250	0.0025	0.017 ^a							
				A*24~B*35	0.0250	0.0124	0.230							

Abbreviations: B-Thal, B-thalassemia; HLA, human leukocyte antigen; p_b , corrected p -value.

^aNo significant p_b after Bonferroni correction.

were described in cell lines from individuals of diverse ethnic origins [7, 8].

On the contrary, given their European/Mediterranean ancestry, the 8.1 AH, characterized by, among others, the alleles HLA-A*01, HLA-B*08, HLA-DRB1*03, HLA-DQB1*02, and HLA-DQA1*05 [7], was found among the most frequent HLA haplotypes in β -Thal patients, being the three most frequent A*01-B*08-DRB1*03, A*24-B*35-DRB1*11, and A*30-B*13-DRB1*07. None of them have been previously described in β -Thal.

A better knowledge of the inter-ethnic HLA haplotype diversity could allow to better understand the association of clinical complications with the disease itself (sickle cell disease or β -thalassemia), as already shown by valuable studies [27–29]. Nevertheless, such possibility was not possible for the present study given the relatively small sample size herein analyzed.

Comparing the most frequent HLA haplotypes of our two populations, we observed that the eight most frequent haplotypes in SCD patients were very different from the ones found in β -Thal patients, and none of them coincided. This difference could be attributed to their different ancestries. SCD patients transplanted in Europe are mainly Black individuals originating from sub-Saharan Africa. On the other hand, β -Thal is the most common form of thalassemia among populations of Mediterranean, North African, and South Asian ancestry. Previous comparisons of genetic distances and haplotypes with other populations have already shown that the Moroccans, North Africans, and Europeans are genetically closer to each other, but distant from sub-Saharan Africans [11, 30].

Our study shows that there is great haplotype variability in patients with hemoglobinopathies and stresses the differences between populations, suggesting that the probability of finding unrelated donors for these patients is hampered by such diversity. HLA alleles and haplotypes widely differ according to geographical areas and ethnicities [31–33], with Black individuals from Central or South America being least likely [34, 35] to have a donor identified in unrelated donor registries. Moreover, as previously stated, sub-Saharan population groups are characterized by greater genetic differences between them than those observed between European populations. This diversity hinders finding HLA-matched unrelated donors for African patients in need of an allogeneic transplant. Even now, there is a paucity of studies that evaluated the distribution of HLA haplotypes in hemoglobinopathies [18, 19], and there is a total lack of information concerning the potential implications of HLA haplotypes in the risk of having the disorders, as well as their contribution in the clinical expression of the diseases.

We must acknowledge that our study includes a relatively small number of highly selected transplanted patients, and that a larger study involving more patients may modify the present findings in terms of HLA diversity and disease associations. Studies considering high-resolution HLA typing and HLA-C data are lacking and could be of interest in the same context of the current study. These limitations are mainly due to the retrospective, observational, and multicentric nature of our study, performed on a niche population. Moreover, despite us being aware that HLA might provide a functional definition of the outcomes of HCT, such as graft-versus-host disease (GVHD) or

infections, the excellent results of HLA-identical sibling donor HCT in the studied populations precluded the evaluation of associations between the different HLA haplotypes and outcomes after HCT.

This study confirms that the genetic diversity of HLA in SCD patients poses practical challenges for finding HLA-matched unrelated donors. This problem seems less accentuated in patients with β -Thal who are genetically closer to the Caucasian populations, and therefore similar to the majority of donors currently available in unrelated donor registries and umbilical cord blood banks. Our results underline the importance of increasing the recruitment of potential donors of African descent in hematopoietic cell donor registries and cord blood banks.

AUTHOR CONTRIBUTIONS

Ryad Tamouza, Eliane Gluckman, Graziana M. Scigliuolo and Wahid Boukouaci designed the study. Graziana M. Scigliuolo, Wahid Boukouaci and Barbara Cappelli analyzed results. Fernanda Volt and Monica Rivera Franco reviewed the data. Graziana M. Scigliuolo wrote the first draft of the manuscript. All authors contributed to the writing and approval of the last version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest.

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

DATA AVAILABILITY STATEMENT

Data supporting the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

This study was approved by Eurocord and SFGM-TC institutional review boards. This study was conducted in accordance with the principles of the Declaration of Helsinki. Patients gave their informed consent to the use of their clinical data to the centers where they underwent the transplantation.

PATIENT CONSENT STATEMENT

The authors have confirmed patient consent statement is not needed for this submission.

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