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ORIGINAL RESEARCH

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The pivotal role of HbA1c assay to detect hemoglobinopathies: A 5-year observational retrospective study in the population of Southern France

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Abstract

Background and Aims: Mobility and migration flows are growing from different countries of the world to European countries, including France and in particular the Mediterranean basin. This study aimed to investigate the presence of hemoglobin (Hb) variants in outpatients/inpatients of the Montpellier Hospital (France) in whom an HbA1c assay had been performed and for which the country of birth had been informed.

Methods: This is a retrospective study from January 2016 to December 2020 based on all high-performance liquid chromatography (HPLC) chromatograms (Tosoh Bioscience HLC-723G8) having an alarm of suspected Hb variant during HbA1c measurement. The corresponding samples were systematically sent to the hematology laboratory for confirmation and identification of Hb variant. Patient's medical history, clinical and demographic data were extracted from each medical chart. Statistical analyses were performed using XLSTAT® software, version 2016.06.35661.

Results: Three hundred sixty-three patients were confirmed with Hb variant exhibiting 17 different Hb profiles, highlighting the pivotal role of glycated hemoglobin (HbA1c) as a detection step. The prevalence of Hb variant in this southern French population was 0.71%, with the highest frequency for the beta-globin variants (n = 342/363; i.e., 94.2%), including the most common: S, C, E, and D in 200/342 (58.5%), 83/342 (24.3%), 29/342 (8.5%), and 11/342 (3.2%), respectively. Among patients with Hb variants, almost half (165/363; i.e., 45.4%) were born in the African continent with a predominance for Morocco (32/165; i.e., 19.3%) and Algeria (29/165; i.e., 17.5%).

Conclusion: HbA1c assay is a useful tool to detect Hb variants. Hemoglobinopathies are a public health issue in the current French population which is a multiethnic society. Despite the monocentric nature of our study, we note a high frequency of

Hb variants in the south of France, which underlines the importance of screening for Hb variants in the whole population.

KEYWORDS
France, hemoglobin variant, hemoglobinopathy screening, migrations

1 | INTRODUCTION

Glycated hemoglobin (HbA1c) is used to diagnose and manage patients with diabetes.[1] A1c assays are based on immunoturbidimetric or separative methods such as high-performance liquid chromatography (HPLC) and capillary electropohoresis (CE). Whereas the presence of a hemoglobin (Hb) variant is undetectable with immunoturbidimetric assay, it is easily suspected using chromatogram or electrophoregram.[2] This notion is of great importance, first because in the presence of Hb variants, the value of HbA1c should be interpreted with caution and second because it allows incidentally to discover Hb variants. Indeed, there has been an awareness of the impact of hemoglobinopathies on morbi-mortality for several years, and therefore on the importance of their screening. This is why a worldwide hemoglobinopathy screening program has been proposed for a long time.[3-4] Hemoglobinopathies are a global health concern affecting over 70% of countries in the world with an Hb variant estimated to be present in 7% of the world's population.[5] The Hb variant is one of the most frequent monogenic inherited disorders with up to 1800 variants described,[6] four of which being widespread: HbS, HbE, HbC, and HbD, with a specific geographical distribution. HbS is mainly prevalent in populations of African descent, whereas HbE is more common in the Asian population. Some rare variants have a minimal pathogenic effect per se, but if associated with another abnormal Hb may lead to severe sickle cell disease (SCD) for example, SCD increasing the risk of mortality.[7]

The resident population in France and particularly in the Mediterranean basin is multi-cultural and multiethnic, due to a significant migration predominantly from Africa continent, which has accelerated over the past 20 years. Due to these migratory flows, the presence of Hb variants has become a major health concern in France as well as in other European countries. In France, a targeted neonatal screening program is in place since 1995 for all newborns defined as being "at risk" for SCD based on ethnic origins,[8] but is not exhaustive due to the declarative nature. As, most heterozygous Hb variants are clinically silent, they are often discovered incidentally if not detected through newborn screening. In this context, HbA1c assay using separative methods may have a pivotal role, especially for silent heterozygous detection.

To detect patients with hemoglobinopathies in the south of France and to test the possibility of using glycated Hb tests to identify such patients, we performed a retrospective observational study among patients attending Montpellier University Hospital for whom an HbA1c test revealed an abnormal Hb profile.

1.1 | Patients

We performed a retrospective descriptive study recording the presence of an Hb variant in outpatients/inpatients older than 1 year having an HbA1c assay at the Montpellier University Hospital (France), between January 2016 and December 2020. Among the HbA1c requests during this period, we selected all HPLC chromatograms with an alarm of Hb variant suspected (Hemoglobin-Variant [H-V]). For patients under 65 years, samples were sent to the hematology department for confirmation and characterization of the variant. If patients were over 65 years, the suspected anomalies were only mentioned in the HbA1c report (Figure 1). This protocol was approved by the local Ethic Committee of Montpellier.

1.2 | Method for HbA1c determination

In our lab routine, HbA1c was measured on the Tosoh Bioscience HLC-723G8 (Tosoh G8) ion exchange HPLC method in variant mode using the Piano software (Tosoh Biosciences) according to the manufacturer's instructions. Briefly, Hb is separated into six different fractions: A1A, A1B, F, Labile A1C+ (LA1C +), Stable A1C (SA1C), and A0, clearly resolved with a time run of 1.6 min per sample, using three positively charged buffers. The presence of major Hb variants, HbS, HbE, HbC, and HbD lead to an abnormal chromatogram with an H-V alarm. Samples with heterozygous HbS, HbC, or HbD exhibit an additional peak over 30% after the A0 peak reported as H-V1, H-V2, H-V0, respectively, and excluded for HbA1c determination. By contrast, samples with heterozygous HbE exhibit an additional small peak between the SA1C and A0 peaks, designated as "Presence of Hemoglobin Variant-E" (PHV-E). All samples with an H-V alarm from patients not previously known to have Hb variant and under the age of 65 years, were sent to our hospital hematology laboratory for further identification.

1.3 | Identification of Hb variants

The Hb variant was characterized using at least three different methods. These include HPLC (Variant II, beta-thal short program, Bio-rad, Hercules),[9] capillary electrophoresis (CE)[10] (Minicap, Variant Hb, Sebia), and isoelectric focusing (Resolve hemoglobin kit, Perkin Elmer). When HbS was suspected, the Itano test was used as a third identification method.[11] For other frequent Hb variants such as Hb C and E, acidic pH electrophoresis (Hydragel Acid Hemoglobin, Sebia)

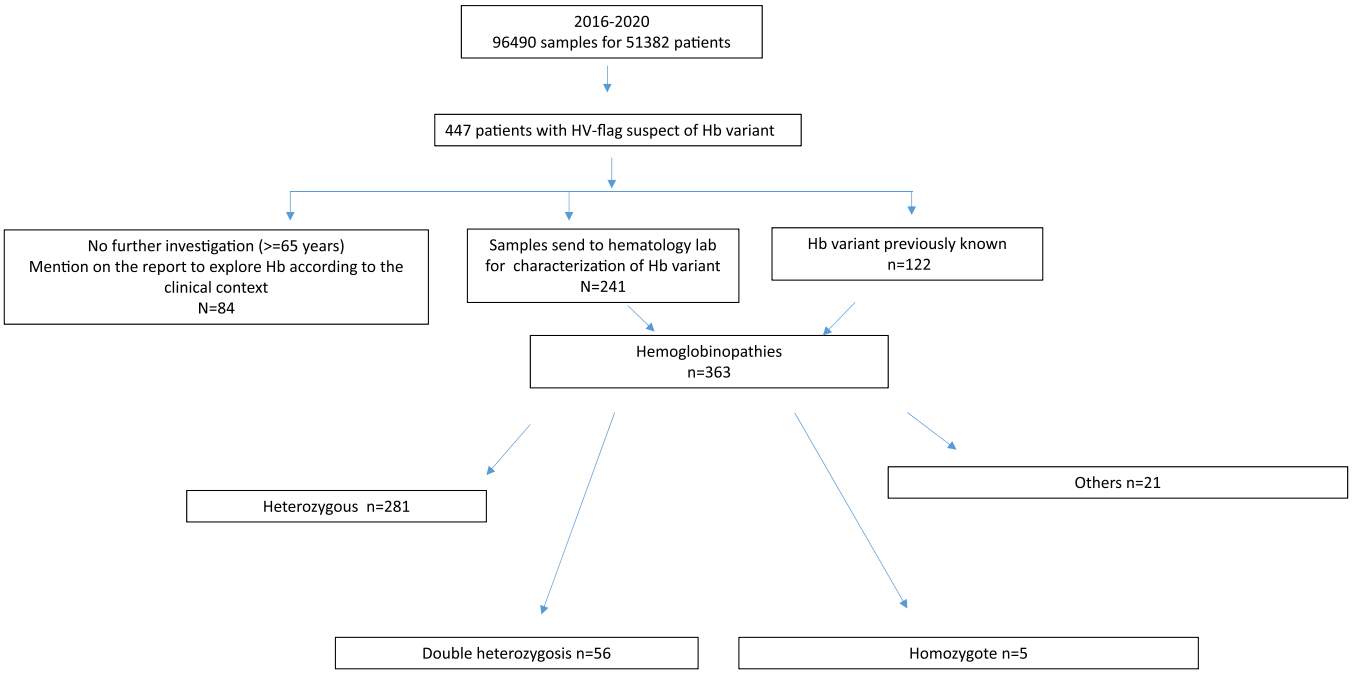

FIGURE 1 summarizing the different steps of selection of patient samples.

was also performed as an additional method. The results of Hb fraction analysis were systematically interpreted using the complete blood count and any other medical information available in the patient's file such as the clinical context of HbA1c request, the country of birth, the notion of blood transfusion, and iron status. For rare variants or supposed complex variant Hb associations, or if thalassemia syndrome was suspected, a genetic analysis (alpha and or beta-globin gene clusters), requiring the signature of an informed consent by the patient according to the French regulation on genetic tests, was proposed to the patient. Analyses of the alpha or beta globin gene clusters include Sanger sequencing of the alpha/beta globin genes and Multiplex Ligation-dependent Probe Amplification (MLPA) from MRC Holland searching for large rearrangement.

1.4 | Statistical analysis

We classified the patients with abnormal HbA1c profiles into three categories (i) Hb variant previously identified; (ii) Suspected Hb variant requiring further investigation; (iii) Suspected Hb variant without further investigation. This latter category corresponds to patient over 65 years for whom no exploration was a common decision between biologists and clinicians.

Newly confirmed Hb variants and those previously known constituted the group "Hemoglobinopathies" including heterozygous, compound heterozygous, and homozygous profiles.

Qualitative variables were expressed as number (percentages). Quantitative variables were expressed as mean (standard deviation, SD) or median (with 25th and 75th percentiles) according to their distribution which was tested with the Shapiro–Wilk statistic.

Statistical analyses were performed using XLSTAT® software, version 2016.06.35661 and GraphPad Prism 8.0.1. (GraphPad Software).

2 | RESULTS

During the 5-year study period, HbA1c was measured by TOSOH G8 in 96,490 samples corresponding to 51,382 outpatients/inpatients. The study workflow is presented in Figure 1. An alarm for abnormal peaks occurred in 447 patients. Of these 447 suspected abnormal Hb profiles, 122 patients had a previously known Hb variant. A total of 241 incidental findings were further investigated to characterize the Hb variant, while 84 cases corresponding to elderly patients (mean age 74.68 ± 6.8), without clinical manifestation, were not further explored. The medical chart of 363 patients with a proven hemoglobinopathy, representing 0.71% (363/51382) of the patients having an HbA1c test, was studied.

Table 1 shows the details of Hb variants for the 363 patients; 174/363, that is, 47.9% were females and 189/363, that is, 52.1% were males (sex ratio M/F:1.10). We identified 17 different profiles. The beta-globin variants were the majority ones ($n = 342/363$; i.e., 94.2%), notably the most common Hb variants: S, C, E, and D were present in 200/342 (58.5%), 83/342 (24.3%), 29/342 (8.5%), and 11/342 (3.2%) samples, respectively. Among the 281 heterozygous patients, the clinical context of detection of the Hb variant could be different[1]: during a medical check-up ($n = 209$), [2] during an exploration of diabetes ($n = 58$), and [3] when gestational diabetes was suspected ($n = 14$). The large majority of cases were asymptomatic heterozygotes ($n = 281$) with an averaged HbA level close to 60%.

TABLE 1 Main characteristics of our population with origin country of birth.

Main hemoglobinopathies	*n*	Native country of birth, *n* (%)	Number of females, *n* (%)	HbA,%	Hb Variant,%	HbF,%	HbA2,%	HbA1c,%
Sickle cell syndrome	212							
Heterozygous Hb S	159	From Africa: 120 (56.6) From FMB: 73 (34.4) From Other countries: 19 (8.9)	79 (49.6)	57.2 [55.6-60.3][a]	38 [35-39.8][a]	1 [1-1][a]	3.3 [3.1-3.8][a]	5.6 [5.2-6.5][a]
Hb S-alpha thalassemia	19		9 (47.3)	61.7 [60.4-65.0][a]	33.4 [31.2-34.7][a]	1 [1-1][a]	3.3 (± 0.5)[b]	6.2 [5.5-7.5][a] (1 ND)
Hb S-bêta thalassemia	22		12 (54.5)	21 [0-56][a]	71.4 [56-80.3][a]	2.7 [1.1-11.2][a]	3 [2.3-3.6][a]	7.3 (± 3.1)[b] (10 ND)
Composite heterozygosity								
HbS/C	8		4 (50)	0.0 [0.0-0.0][a]	47.5 [44.9-48.3][a]	2.2 (± 2.1)[b]	3.4 (± 0.5)[b]	ND
Homozygous HbSS	4		2 (50)	66.4 (± 29)[b]	28.6 [5.9-60.1][a,c]	2 [1-13.3][a]	3.2 (± 0.3)[b]	ND
Hemoglobin C	83							
Heterozygous Hb C	80	From Africa: 40 (48.2) From FMB: 38 (45.7) From Other countries: 5 (6.0)	36 (45)	55 [53.3-58.3][a]	40.9 [37.9-42.7][a]	1 [1-1][a]	3.1 (± 0.3)[b]	5.7 [5.3-6.5][a]
Hb C-alpha thalassemia	3		1 (33.3)	63 (± 4.9)[b]	32.2 (± 4.9)[b]	1.1 (± 0.2)[b]	3.6 (± 0)[b]	5.5 (± 0.6)[b]
Hemoglobin D	11							
Heterozygous Hb D	8	From Africa: 1 (9.0) From FMB: 9 (81.8) From Other countries: 1 (9.0)	6 (75)	57.5 (± 2.2)[b]	38.6 (± 2)[b]	1 [1-1][a]	2.9 (± 0.5)[b]	6.5 (± 1)[b]
HbD-Punjab	3		1 (33.3)	57.1 (± 0.2)[b]	38.8 (± 0.2)[b]	1 (± 0)[b]	3.1 (± 0.2)[b]	6.5 (± 1.2)[b]
Hemoglobin E	29							
Heterozygous Hb E	25	From Asia: 12 (41.3) From FMB: 16 (55.1) From Other countries: 1 (3.4)	8 (32)	72.1 [70.9-73.1][a]	24.4 [23.5-25.4][a]	0 [0-0.6][v]	3.1 (± 0.5)[b]	6.3 (± 1.1)[b] (8 ND)
Hb E-alpha thalassemia	4		1 (25)	75.4 (± 4.9)[b]	21.6 (± 4.9)[b]	0 (± 0)[b]	3.1 (± 0.2)[b]	6.0 (± 0.5)[b]
Others								
Persistence of HbF	7	From Africa: 2 (28.5) From FMB: 5 (71.4)	3 (42.8)	86.4 (± 11.6)[b]	NA	10.4 (± 9.3)[b]	1.9 (± 0.3)[b]	5.5 (± 0.9)[b]
HbJ	3	NK	1 (33.3)	46.4 (± 4.8)[b]	48.1 (± 4.1)[b]	3.1 (± 0.7)[b]	2.4 (± 0.1)[b]	ND
HbG san Jose	1	Algeria	1 (100)	61	35.3	1	2.7	6,3
HbO-arab	2	From Africa: 1 (50.0) From FMB*: 1 (50.0)	2 (100)	57 (± 2)[b]	38.9 (± 1.8)[b]	1 (± 0)[b]	2.7 (± 0.4)[b]	6.3 (± 1.5)[b]

TABLE 1 (Continued)

Main hemoglobinopathies	*n*	Native country of birth, *n* (%)	Number of females, *n* (%)	HbA,%	Hb Variant,%	HbF,%	HbA2,%	HbA1c,%
Bêta thalassemia homozygous	1	Madagascar	0	0	NA	1	2.8	ND
Nonidentified variants	14	From Africa: 6 (42.8) From FMB: 7 (50.0) From Other countries: 1 (7.1)	6 (42.8)	76.9 (± 15.5)[b]	20.7 (± 15.2)[b]	1 [1-2.5][a]	2.3 (± 0.9)[b]	6.1 ± [5.3-8.4][a] (3 ND)

Abbreviations: FMB, french mediterranean basin; Hb, Hemoglobin; NK, not known, NA, not applicable, ND, not determined; SD, standard deviation

[a]Data expressed as median [25th-75th percentile].

[b]Data expressed in mean ± SD.

[c]Data on transfusion were not available.

HbA2 was detected in all patients. HbA1c was ≥6.5% for 112/363, that is, 31%. All the severe forms of hemoglobinopathies (n = 61) were homozygous or compound heterozygous patients: 12 with SCD, including 4 HbSS and 8 HbSC subjects, as well as one case of homozygous beta thalassemia. A total of 83 genetic tests were performed.

Hb variants were predominantly observed in adults (n = 325/363, i.e., 89.5%) who were born either in a country other than France or in the French Mediterranean basin. For 44/363 (12%) patients, identification of the Hb variant was made by newborn screening or in the presence of clinical manifestations in the newborn or in childhood, in their country of birth, including France, Africa, or other countries. Upon arrival in our institution, these children underwent a clinical and biological assessment.

Figure 2 summarizes the distribution of Hb variants in our population according to the country of birth. For 165/363 (45.4%) of the identified variants, the patient originated from an African region with a predominance for Morocco (32/165, i.e., 19.3%) and Algeria (29/165, i.e., 17.5%). The HbE variant was predominantly observed in individuals with Asian origins. In Supporting Information: figure A, we reported HPLC profiles for the most frequent Hb variant.

3 | DISCUSSION

In this study, we reported Hb variants detected through HbA1c assay over a 5-year period. All samples with an alarm of Hb suspecting variants were further confirmed by hematology department using three methods, highlighting the powerful screening of Hb variant through separative HbA1c assay. In addition, all samples with previously known variants (n = 122) were identified as suspects during A1 test, confirming the robustness of this test and suggesting that analysis of HbA1c could be a useful test for the diagnosis of diabetes as well as the risk of developing diabetes [1] and hemoglobinopathies.[12] So, we found a proportion of 363/51382, that is, 0.71% in a selected population having an HbA1c test, close to the data from Angastiniotis et al.[13] In Europe, four distinct groups of countries were observed, those that were endemic for hemoglobinopathies (Cyprus, Greece, Italy), those with a long history of hosting migrants (France, United Kingdom), those with low immigration (Denmark) and finally those with recent immigration phenomenon (Spain).[13-14] In the two first situations, the hemoglobinopathy alleles were endogenous since people of these regions correspond to the second, third, or even fourth generation.[13] Carriers of Hb disorders represented 15%, 8.70%, and 6.5% of the total population in Cyprus,[13] Greece, and Italy, respectively; 0.65% and 0.58% in France and United Kingdom, respectively, and 0.34% in Denmark. In Spain, the rate of carriers of Hb disorders in the general population was 1.90%, highlighting the fact that carrier frequency was rising most rapidly in this country with recent immigration. The migratory flow from the African continent was mainly directed toward Spain and Italy, Africa being a neighboring country. According to Angastiniotis et al.,[13] France was influenced by migrations from sub-Saharan Africa

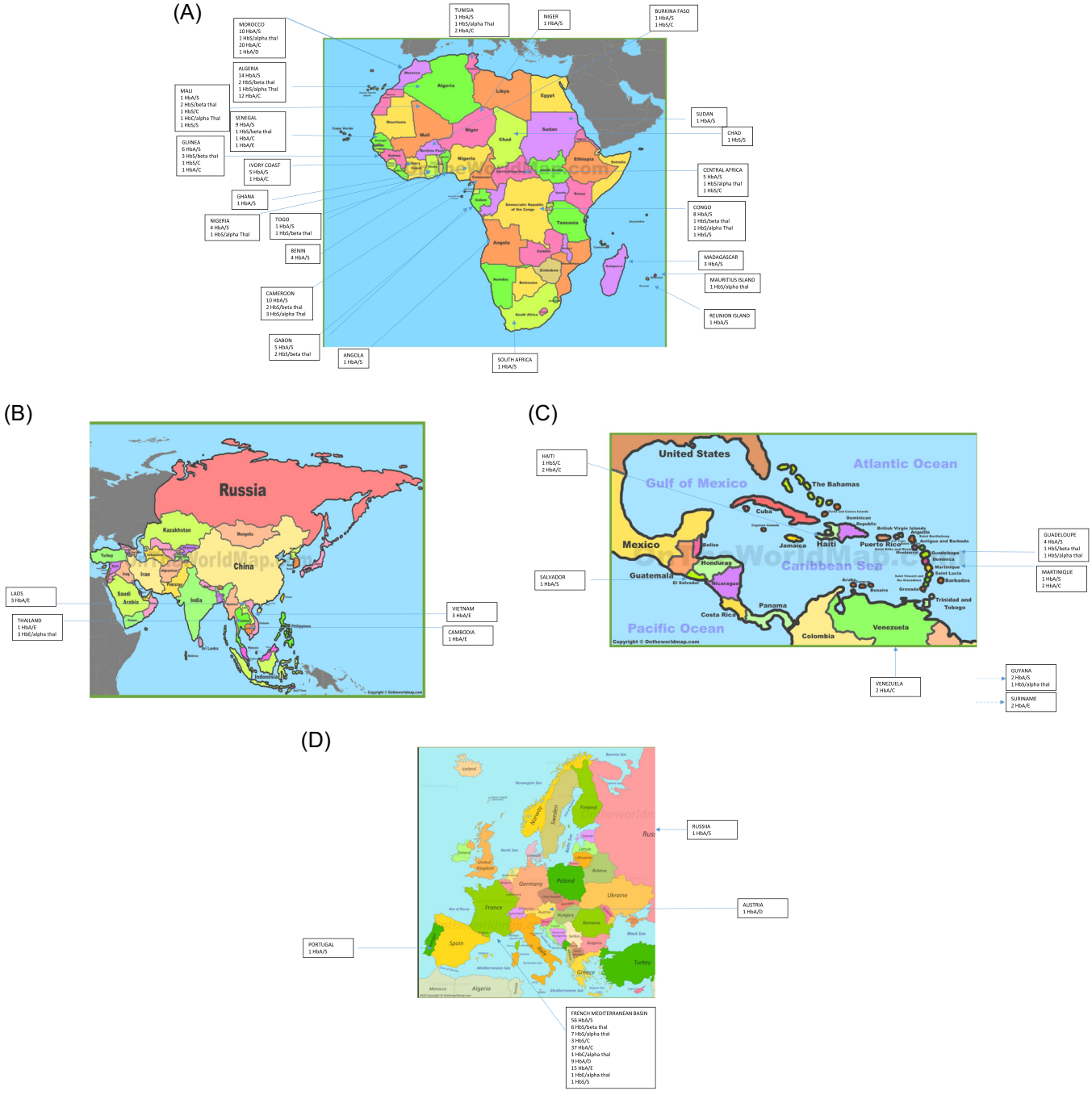

FIGURE 2 Distribution of hemoglobinopathies of our population according to country of birth (A) from African continent (B) from Asia (C) from Overseas and (D) from French Mediterranean basin. Hb, Hemoglobin; thal, thalassemia.

and more recently by those from Southern and Eastern Europe, West Pacific, and Asia. As previously described,[15] the majority of the variants identified in our study came from Africa, particularly the HbS and C, and from Asia for the HbE variant. Screening studies carried out in European countries (i.e., Greece, Italy, Portugal, and Spain) also found HbS as the most frequent hemoglobinopathy.[16] However, the incidence of hemoglobinopathies (i.e., the proportion of carrier immigrants compared with the total population) is variable among countries since, unexpectedly, the incidence is lower in Spain (0.33%),[17] than in other Mediterranean countries, but also than in France (0.54%), United Kingdom (0.48%), and Belgium (0.65%).[13,16] This could be explained by the fact that the migration to Spain is a new phenomenon (over the past 20 years) unlike in other European countries where migrations started 60 years ago.[14,16] In view of the increasing population movements, the level of prevention and management of hemoglobinopathies is not the same in all countries. Therefore, these disorders are under-estimated and several WHO resolutions, as well as European Union (EU) directives on migrant

health, were introduced.[18-19] In addition, the prevalence of these disorders varies considerably between the different regions of the world, between countries in the same region, between areas within a country and even between different medical centers within the same area.[16] Recently, a Chinese study[20] reported that HbE was the most frequent variant (20.8%) followed by Hb New York (14.9%), Hb-J Bangkok (10.6%), and Hb Q-Thailand (9.6%), while the other three common Hb variants worldwide (i.e., HbS, HbC, and HbD) were rare in Southern China.

Our study had one main limitation related to the selection of the population in the context of monitoring or exploration of diabetes, but highlighted several general remarks:

1. the HbS variant is predominant in the South of France,
2. the heterozygous Hb variant discovery is often fortuitous,
3. given the prevalence of Hb variants, it is recommended to always perform a first HbA1c assay with an HPLC or CE method instead of an immunoturbidimetric method or point-of-care test,
4. laboratories should systematically report the presence of an Hb variant, as HbA1c thresholds are not currently validated in the presence of variants,
5. HbA1c assay is inappropriate in case of a homozygous Hb variant or compound heterozygosity: it is important to educate clinicians not to request an HbA1c assay in these cases.

In conclusion, this study evidenced that separative methods for HbA1c test are very useful for the incidental detection of Hb variants. It revealed the presence of a Hb variant in 363/51 382 (i.e., 0.71%) patients of a selected population of the South of France, having an HbA1c test, with a predominance of heterozygous HbS. The detection of variants of clinical relevance, especially HbS, being associated with a reduced morbidity and mortality, therefore a screening should be encouraged and extended to all populations as soon as possible. Families with a genetic risk for the presence of a clinically relevant Hb variant should also require a family screening.[21] Systematic screening for SCD in all newborns in France is scheduled in 2024 as recently announced by the Haute Autorité de Santé.[21]

AUTHOR CONTRIBUTIONS

Anne M. Dupuy: Conceptualization; formal analysis; funding acquisition; investigation; methodology; writing—original draft. **Jean P. Cristol**: Conceptualization; supervision. **Anne S. Bargnoux**: Methodology; resources; validation. **Maelle Plawecki**: Formal analysis; methodology; resources. **Manuela Lotierzo**: Methodology; resources. **Patricia Aguilar-Martinez**: Conceptualization; supervision; visualization; writing—review & editing. **Stéphanie Badiou**: Conceptualization; investigation; methodology; supervision; writing—original draft.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

TRANSPARENCY STATEMENT

The lead author Jean Paul Cristol affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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