<u>Minireview Article</u>

Systematic review of genetic-related risk factor and inhibitor epidemiology in people with severe hemophilia A from Africa: A 2023 update

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ABSTRACT

Background and Aims: Prevalence of factor VIII inhibitors in patients with haemophilia A varies from study to study, ranging from 15% to 30%. The important risk of inhibitor development is factor VIII mutation responsible for haemophilia A. Few studies have reported factor VIII mutations in Africa. The aim of this study was to review on factor VIII mutations of severe haemophilia A in Africa, and those associated with inhibitor development.

Study design and methodology: A systematic review was carried out using the electronic databases Pubmed, Science Direct, Index Medicus Global and African Journals online and the key words "haemophilia A", "inhibitor", "genetic" and "Africa". Studies written in French or English on the African continent and published between 2012 and 2023 were included. Publications relating to acquired haemophilia and duplicates were excluded. In the end, 17 articles were selected.

Results: The factor VIII mutations involved in severe haemophilia A in Africa are variable, consisting of intron 22 inversion, large or point deletions, nonsense and missense mutations and splicing abnormalities. Among the latter, numerous previously unrecorded mutations have been identified, and a single case of intron 1 inversion has been found in Algeria. Prevalence of factor VIII inhibitors in severe haemophilia A in Africa varies between 23% and 30%. Genetic abnormalities associated with inhibitors include intron 22 inversion, large deletions such as exon 1-13 deletion, nonsense mutations and c.1010-2A>G mutation.

Conclusion: A better knowledge of the factor VIII mutations involved in severe haemophilia A in Africa will help improve patient management.

Keywords: Hemophilia, Haemophilia, Factor VIII, inhibitor, genetic mutations, Africa

1. INTRODUCTION

Haemophilia A is an X-linked bleeding disorder caused by a mutation in factor VIII gene and affecting at birth 24,6% cases for all severities of 100,00 males [1]. It is the most common of the inherited bleeding disorders. Haemophilia affects men and women are usually carriers. The amount of residual clotting factor VIII defines three clinical and biological forms: mild haemophilia A (6IU/dL to < 40%), moderate haemophilia A (1- 5IU/dL), and severe haemophilia A (< 1UI/dL). [2]. Classically, patients with severe form of haemophilia A are prone to joint and muscle bleeds [3]. External bleeding after deep cutaneous lesions, mucous membrane bleeding (epistaxis, gingivorrhagia) or visceral bleeding (haematuria) may also be observed. Nowadays, the standard of care in patients with severe haemophilia A is primary prophylaxis. For many years, replacement therapy has been based on concentrated factor VIII injections, either on demand in the event of a bleeding episode or as prophylaxis [2]. The most challenging complication of this treatment is development of inhibitory alloantibodies which neutralize activity of FVIII, compromising the efficacy of the treatment [4]. Detection of these inhibitors is an integral part of the standard laboratory follow-up of haemophilia, and its prevalence varies from study to study in haemophilia A, ranging from 15% to 30% [5]. This prevalence is four times higher in severe haemophilia A [5], and one of the most important predictors of the risk of inhibitor development in severe haemophilia A is the F8 gene mutation type [6-8]. Few studies have reported F8 gene mutation type for haemophilia A in Africa. The aim of this study was therefore to review the literature on F8 gene mutation type in Africa and to study those associated with development of inhibitors. Our data were then compared with mutations reported in caucasian populations.

2. METHODOLOGY

We tried to identify all published studies that defined F8 gene mutation type in Africa and all studies on development of inhibitory alloantibodies against FVIII. We carried out a systematic literature review using the electronic databases PUBMED, Science Direct, Index Medicus Global and African Journals online and the key words "haemophilia A", "inhibitor", "genetic" and "Africa". A manual search was then carried out using the bibliographic references of the detected articles to identify other relevant publications. Full-text studies written in French or English, published from 2012 to 2023 and focusing on African patients with haemophilia A were included. Selected articles included information on the different variants of FVIII gene mutation type and/or genetic abnormalities associated with inhibitor development in one of the African countries. Articles describing the sociodemographic, clinical and biological characteristics of African haemophilia A patients who have developed inhibitors, as well as the prevalence of these inhibitors, were also retained.

On the other hand, articles relating to acquired haemophilia A or those dealing with constitutional haemophilia A but carried out outside Africa, as well as duplicates, weren't retained. The same applies to annotations or comments not reporting clinical cases. Of the 1956 articles identified, 17 were finally retained (Figure 1)

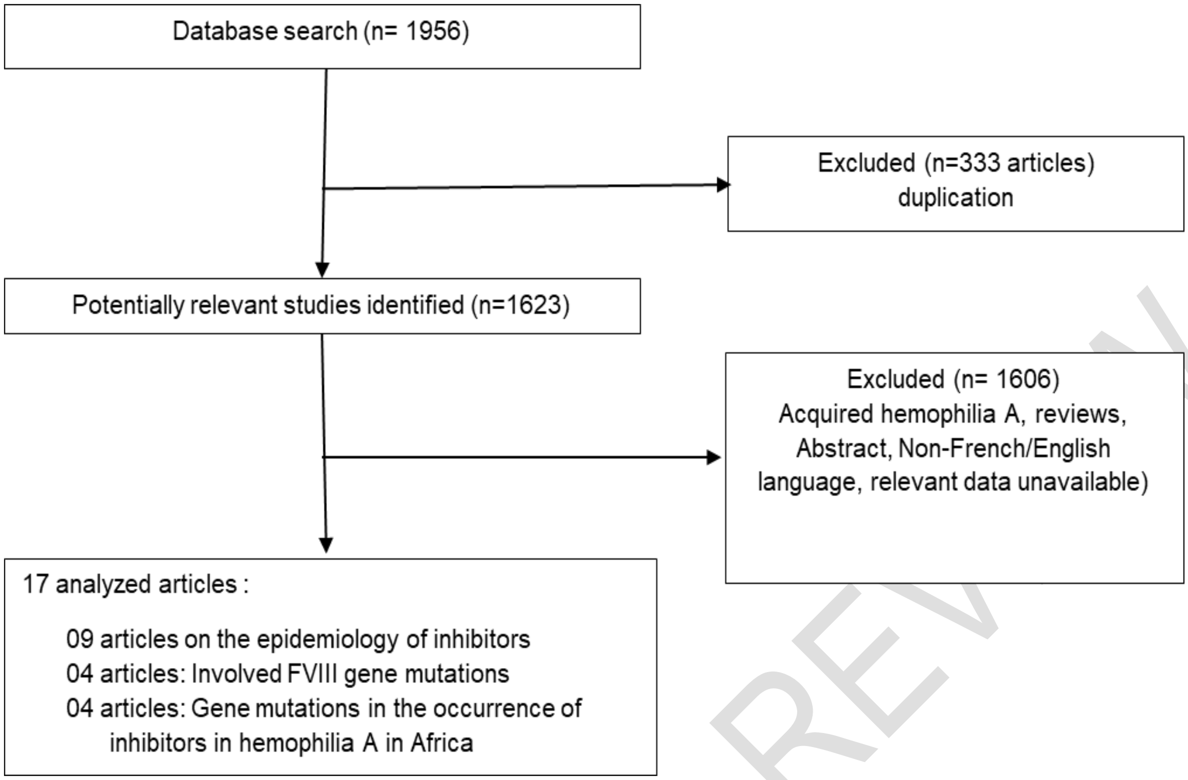

Figure 1: Flowchart of the inclusion of studies.

3. RESULTS

1- Study characteristics

Overall, we identified 17 references through the electronic and hand searches that met the inclusion criteria and which were considered for this systematic review. Nine of these references, had studied the epidemiology of inhibitors in haemophilia A encountered in different African countries [9-17]. Four articles studied the factor VIII gene abnormalities involved in haemophilia A in Africa, and four others reported the FVIII gene variants associated with inhibitor development in haemophilia A [9, 18-20]. Studies were carried out in four Northern African countries (Morocco [12], Tunisia [16], Algeria [19] and Egypt [20]), two West African countries (Senegal [9, 10, 17] and Côte d'Ivoire [15, 18]), one Central African country (Cameroon [13]) and South Africa [11, 14].

2- F8 gene mutations profile in hemophilia A in Africa

The DNA extraction methods used varied from study to study. Some authors used organic solvents (phenol chloroform) [14, 23], while others used ion-exchange resin microcolumns [7, 16].

Molecular techniques used to identify FVIII gene mutation responsible for haemophilia A in Africa also varied from one publication to another: Detection of intron 22 inversion was carried out by Long Range PCR (Senegal, Côte d'Ivoire, Algeria, Tunisia) [7, 14, 16, 23] or by Inverse Shifting PCR (IS PCR) in Egypt [29]. Sometimes, research teams from the same country had used different molecular techniques. This is the case in Egypt, where Mosaad MR et al used IS PCR in Cairo [29], while Sherief LM et al used Long-Range PCR in Zagazig [18].

In the case of severe haemophilia, detection of intron 22 inversion was carried out as a first step, and in its absence, the search for intron 1 inversion was a second step. In the absence of intron 22 and intron 1 inversions, sequencing has been performed by all authors, most of them using the latest sequencing techniques [7, 16, 23, 29, 30].

At the end of these different strategies, various FVIII gene mutation type listed in databases such as HAMSTERS or EAHAD [28], like intron 22 inversion, intron 1 inversion, point mutations and large rearrangements, were found in Africa.

The frequency of intron 22 inversion of the factor VIII gene varies widely from one study to another and from one region of Africa to another. This mutation is reported in 36% [9], 38% [7] and 39.5% of severe PwH A [16] in South Africa, Senegal and Côte d'Ivoire respectively. However, in studies from Northern Africa such as Algeria and Morocco, intron 22 inversion appears to be more frequent, with frequencies of 89% [23] and 42.8% [10] respectively. Inversion of intron 1, on the other hand, is rare, with only one case reported in Algeria [17]. This mutation wasn’t reported in any of the other studies, notably in Egypt, Tunisia, Côte d'Ivoire and Senegal.

Other mutations of the factor VIII gene were point mutations involving substitution, deletion, insertion, or inversion of one or more nucleotides. These mutations varied and found in all populations studied, resulting in nonsense mutations, missense mutations, or splicing alterations within the FVIII gene. In addition, frameshift mutations have been identified in six severe PwH A from Côte d'Ivoire [16], and two from Egypt [29]. The same applies to large FVIII gene deletions identified in Senegal and Côte d'Ivoire [7, 16].

However, mutations not reported in the HAMSTERS and EAHAD databases have also been identified in several African countries. In addition, no mutations were found in some PwH (Table 1).

Table 1 lists the number of patients with the various factor VIII gene variants involved in severe haemophilia A in Africa, as well as the new mutations identified.

Table 1. Distribution of FVIII gene variants and new mutations identified in severe hemophilia A in Africa

Countries, Years	Study Popula-tion	Number of severe HA	Number of FVIII gene variants in case of severe HA	New mutations in severe HA (HGVS notation)
Tunisia 2012 [21]	28	19	Inv 22 : 7 Inv 1 : 00 others : 12 Non-identified mutations : 00	5 new mutations : – Exons1-13del – c.592 T>C; p.C179(198)R – c.4844ins264pb – c.90-91insA; p.12(31)LfsX11 – c.2409 T>C; p.N784(803)N
Algeria 2014 [22]	24	22	Inv 22 : 13 Inv 1 : 01 Others : 06 Non-identified mutations : 02	02 new mutations – c.5219 þ 1G > T – c.2189G > A
Côte d'ivoire 2020 [18]	54	43	Inv 22 : 17 Inv 1 : 00 Others : 24 Non-identified mutations : 02	5 new mutations : – c.266-?_*1788+?dup – c.1921T > G – c.[4738_4753del; 4754_4771dup] – c.5322_5330del9 – c.6115 + 2T>A
Senegal 2017 [9]	22	21	Inv 22 : 8 Inv 1 : 00 Others : 12 Non-identified mutations : 01	05 new mutations : – c.3655_3659del AAGAA – c.4853dupT – c.3528_3530delinsGA – c.1010-2A>G – c.803A>G

HGVS : Human Genome Variation Society, HA : Hemophilia A

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The involved genetic mutations study in severe haemophilia A is useful both for screening haemophilia carriers and for improving the management of PwH. In fact, the type of genetic abnormality involved in haemophilia is a factor associated with the appearance of anti-FVIII inhibitors. Large deletions and certain missense mutations are thus clearly associated with a high risk of developing an inhibitor [23]. As many authors claim that Africans develop inhibitors more frequently than caucasian PwH [24, 25], it was essential to study the epidemiology of inhibitors in severe haemophilia A in Africa, as well as the genetic mutations in the occurrence of these inhibitors.

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3- FVIII inhibitors epidemiology in haemophilia A in Africa

3-1- Inhibitor prevalence in haemophilia A

Nine studies have determined the prevalence of inhibitors in haemophilia A. This prevalence varied from country to another, ranging from 7.8% in Côte d'Ivoire [15] to 29.2% in Algeria [19]. Among severe PwH A, the prevalence ranged from 4.6% in Côte d'Ivoire to 28% in Cameroon, depending on the series, and around half (45.5% in Morocco) or almost all (Senegal, Tunisia) of PwH who developed inhibitors were severe PwH (Table 2).

Table 2: Prevalence of inhibitors in hemophilia-A in Africa

Countries, Years of publication	Authors	Study population (N)	Number of severe HA	Prevalence of inhibitors	Prevalence of inhibitors in severe HA
Senegal, 2017	Seck M et al [9]	22	21	5 (22,7%)	5 (23,8%)
Ivory Coast, 2019	Lambert C et al [18]	50	-	6 (12%)	-
Ivory Coast, 2018	Lambert C et al [15]	64	43	5 (7,8%)	4 (4,6%)
Cameroon, 2014	Balôgôg PN et al [13]	38	23	7 (18,5%)	7 (30%)
South Africa,2014	Lochan A et al [11]	216	-	29 (13%)	-
South Africa, 2022	Lethukuthula M et al [51]	36	-	18%	-
Algeria, 2014	Zemani-Fodil et al [19]	24	22	7 (29,2%)	6 (27,3%)
Egypt, 2020	Sherief LM et al [20]	120	-	21 (18%)	-
Marocco, 2022	Bouyadmar M et al [12]	95	-	21 (22%)	_
Tunisia, 2000	Ghali O et al [16]	46	23	7 (15,2%)	6 (26%)

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However, prevalence studies do not always include PwH A with transient inhibitors, or patients whose inhibitors have disappeared after immune tolerance, hence the need for incidence studies.

3-2 Inhibitors incidence in haemophilia A patients in Africa

To our knowledge, one study has investigated the incidence of haemophilia in Africa. The study by Touré SA et al in Senegal determined incidence of inhibitors in severe PwH A treated with low-dose factor VIII concentrates for prophylaxis. Over a 3-year period, three of the 13 severe PwH A included had developed inhibitors or an incidence of 23% [10].

4- Factor VIII gene mutations type associated with risk of inhibitor development in PwH A from Africa

Studies on FVIII mutations and inhibitors are scare in Africa, particularly in sub-Saharan Africa. Table 3 lists the FVIII gene mutations associated with inhibitors development in severe HA in Africa.

Among PwH A with intron 22 inversion, 12.5% and 37% respectively had developed inhibitors in Senegal [7] and Egypt [18]. In South Africa, PwH with intron 22 inversion were twice as likely to develop inhibitors (p=0.05) [9], whereas this risk was multiplied by three to four according to Sherief et al in Egypt (p=0.03) [18].

In addition to intron 22 inversion, the examined articles in this review reveal that large deletions were associated with the occurrence of inhibitors, as is the case for the del 1-13 deletion identified in Tunisia [30], as well as del exon 6+7 and del prom + exon 1 found in Senegal [7]. Similarly, the only large deletion identified in Côte d'Ivoire was also associated with inhibitor development [16]. When deletions are smaller, the consequences are variable and may or may not be associated with inhibitor development in haemophilia A [7, 16, 17]. Also, the c.322A>T.p.Lys108 mutation found in Algeria is associated with the occurrence of inhibitors [17].

Furthermore, several mutations implicated in severe haemophilia A and identified in the various African studies weren't listed in the Hamsters and EAHAD databases. Some of these were associated with the occurrence of inhibitors, such as mutations involving the c.1010-2A>G splice site [7] and the large deletion of exons 1 to 13 [30] identified in Senegal and Tunisia respectively.

Table 3: FVIII gene variants associated with the occurrence of inhibitors in severe hemophilia-A in different African countries

Countries	**Mutation (HGVS notation)**	**Type**	**Location**
Tunisia [26]	Exons1-13del	Large deletion	Exon 1- 13
Algeria [19]	inv 22	Inversion	Intron 22
	c.322A>T, p.Lys108	Nonsens	Exon 3
	c.3780G>C, p.Asp1260Glu	Polymorphism	Exon 14
Senegal [9]	Inv 22	Inversion	Intron 22
	c.(670 + 1_671-1)_(1009 + 1_1010-1)	Large deletion	Exon 6
	c.(?_-1120)_(143 + 1_144-1)	Large deletion	Promotor + Exon 1
	c.6049delG	Small délétion	19
	c.1010-2A>G	Splice site	Ivs7
Ivory Coast [18]	c.788+?_1009-?del	Large deletion	Exon 7
	Inv 22	Inversion	Intron 22

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4. DISCUSSION

This literature review describes the different FVIII gene mutations in severe haemophilia A in Africa, and in the occurrence of inhibitors. The term "Africa" is an artificial geographical delimitation, covering socio-economic realities that vary tremendously from one country to another. However, there are many reasons for limiting our analysis to this scale. PwH are under-diagnosed in Africa, accounting for just 3% of PwH worldwide [27, 28]. This situation is probably due to the limited technical resources [27, 29] of medical analysis laboratories and the small number of haemophilia care centres in developing countries [29]. According to a study carried out by Mbanya in 2021, there were three HTCs in Cameroon and five in Senegal [29]. Moreover, considering the limited socio-economic level of patients or their relatives, and the great distance generally separating PwH' places of residence from haemophilia treatment centres, many PwH are treated on demand only in the event of bleeding episodes. And even when PwH manage to find the means to travel to haemophilia treatment centres, many of these centres lack the consumables and reagents needed [30] for factor VIII assay and systematic screening for inhibitors. This may explain very low number of publications on haemophilia in Africa.

However, this review is probably not exhaustive, due to the several studies carried out in Africa, which are difficult for the scientific community to access as they are not referenced in international databases of medical literature.

Prevalence of PwH who developed inhibitors at the review time in Africa ranged from 4.6% to 45.5%, depending on the country. This difference from one country to another is probably linked to the variability of the inclusion criteria used. Some authors included all haemophilia A patients in their cohort, while others included only unrelated haemophilia A patients. Similarly, while many of the PwH included in the various studies were on episodic treatment, the authors included varying proportions of patients on prophylaxis in their cohorts. Thus, these numerous limitations make it impossible to compare published results with each other or to generalize them to the African population. However, the prevalence of inhibitors in haemophilia A found in the various African studies remains similar to those found in the various studies in the literature, estimated at between 3.6% in Great Britain [31] and 26.8% in Greece [32]. In France, the prevalence of inhibitors in haemophilia A, whatever the degree of severity of the disease, was 7% [33]. After analysis of the numerous data from caucasian studies by Wight J et al, the overall prevalence of inhibitors, whatever the severity of the haemophilia, is 5 to 7%. This leads many authors to assert that the prevalence of inhibitors in Africans appears to be higher than in caucasians [8, 34].

All authors agree that mutation of the FVIII gene involved in haemophilia is one of the genetic factors determining the occurrence of inhibitors.

In severe haemophilia A, the search for intron 22 inversions was carried out in the majority of studies using the long-range PCR (LR PCR) technique, except in Egypt where inverted-shifting PCR (IS PCR) was used. The long-range PCR developed by Liu et al [35] is a rapid technique that uses a small quantity of DNA. However, it is technically difficult to standardize and requires a high-quality DNA extract. This has probably motivated the development of alternative methods such as reverse PCR used in Egypt [36, 37] or real-time PCR developed by Kloppers JF in South Africa in 2019 [38, 39].

The results of these different studies have revealed a prevalence of intron 22 inversion that varies from one country to another in Africa, ranging from 36 to 40% for sub-Saharan countries, while this prevalence seems slightly higher in Algeria (57.89%) [22] and Egypt (42.8%) [20]. These different prevalences of intron 22 inversion in the African population remain similar to the prevalence of this same mutation in the Colombian and Mexican populations, which were 42.4% [40] and 45% [41] respectively.

As for intron 1 inversion, it has been systematically investigated in the various studies carried out in Africa using various molecular techniques recommended by the United Kingdom Haemophilia Centre Doctors Organisation (UKHCDO) [37, 42]. But only one case of intron 1 inversion has been identified in western Algeria. This confirms the rarity of this mutation in severe haemophilia A in Africa. However, intron 1 inversion is just as rare in several other studies, such as in Iraq and Pakistan, where the prevalence was 3.3% [43] and 0.77% [44] respectively. This raises the question of the value of systematically searching for this inversion in the African population.

Furthermore, in the absence of introns 22 and 1 inversion in PwH with severe haemophilia A, the FVIII gene sequencing helped to identify several large deletions that were associated with the occurrence of inhibitors, whereas missense mutations were not associated with these anti-FVIII Ac. In addition, our literature review revealed that the sole mutation of the FVIII gene involved in haemophilia A is not sufficient to explain the occurrence of an inhibitor in PwH because two PwH from the same family do not both necessarily develop inhibitors [22]. Other genetic factors such as Human Leucocyte Antigen (HLA) [45-47], haplotype [48, 49] and interleukin 10 [50] may be involved in the occurrence of inhibitors in haemophilia A.

Also, as described by many authors in the literature, no mutation could be identified in certain PwH during studies carried out in Algeria, Egypt, Senegal and Côte d'Ivoire. This could be related either to the performance of the tests or to as yet unidentified mechanisms involved in haemophilia

5. CONCLUSION

The genetic mutations spectrum causing haemophilia is similar in all countries. Intron 22 inversion is likely the most frequent mutation in Africa, and was often associated with the occurrence of inhibitors, but this can also occur without any statistically significant link. However, large deletions were almost always associated with the occurrence of inhibitors, unlike missense mutations, which were in no case associated with the occurrence of anti-FVIII inhibitors in the studies exploited. Nevertheless, it is necessary for all African countries to join their efforts to carry out a multicentric study including a larger study population with a more rigorous study method so as to obtain results that can be generalized to the African population.

ETHICS STATEMENT

Not applicable

Conflict of interest – There should be declaration of conflict-of-interest statement on behalf of the authors

Declaration of the role played by each author in the writing of the article to be documented please.

Acknowledgement – Do you have anyone to thank or acknowledge for example if the tables were taken from some sources then the source of the tables should be acknowledged please.

CONSENT

Not applicable

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