Genetic studies on uric acid and gout in Africa: Where do we stand?

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Sir,

Uric acid is a molecule of interest in medicine, particularly rheumatology. It is best known for its essential role via hyperuricemia in gout, one of the most common causes of arthritis in Africa and worldwide[1]. It has also been shown in recent decades that uric acid is involved in a number of biological processes, including oxidative stress, where it shares an anti- and pro-oxidant duality, as well as chronic inflammation linked to atherosclerosis, hypertension and therefore cardiovascular risk[2-4]. To this end, uricemia can be used as a biomarker for a number of diseases and clinical situations. Uric acid metabolism, and more specifically its biosynthesis and elimination, are regulated primarily by genetic mechanisms[5,6]. Genetic studies are therefore vital in providing a better understanding and use of this molecule in the prevention and management of the diseases with which it is associated, taking into account the diversity of populations. In Africa, there are several studies on uric acid and gout, but genetic knowledge specific to the continent's populations is still poorly understood and needs to be summarized in order to present the state of research and provide prospects for its improvement and future directions. The aim of this study was to assess the contribution of African authors to genetic studies carried out in Africa on uric acid, gout and related disorders.

We carried out a systematic review of the literature searching for appropriate terms relating to uric acid and gout, combined with terms reflecting genetics, and then with the names of the 54 African countries and sub-regions (Supplementary material 1). The search was conducted on PubMed and AJOL on 22 February 2024, with no date or language restrictions. We included studies conducted in Africa and published in the form of original articles (cross-sectional study, case-control study, cohort study, randomised or non-randomised clinical trial). We also included case reports, and letters to the editor reporting original data. We excluded literature reviews, conference abstracts and duplicate publications. Titles and abstracts were independently assessed by two investigators (JRN and ALTK). Discrepancies were resolved by consensus. The articles retained after screening were downloaded and assessed for eligibility, and those retained were included for data extraction (Figure 1).

Supplementary material 1: Search strategy

	PUBMED
#P1	((gout[Title/Abstract] OR «uric acid»[Title/Abstract] OR uricemia[Title/Abstract] OR hyperuricemia[Title/Abstract] OR «crystal, arthropathy»[Title/Abstract] OR tophus[Title/Abstract] OR tophi[Title/Abstract])
#P2	(genetic[Title/Abstract] OR gene[Title/Abstract] OR genotype[Title/Abstract] OR genomic[Title/Abstract] OR allele[Title/Abstract] OR genome[Title/Abstract] OR polymorphism[Title/Abstract] OR mutation[Title/Abstract]))
#P3	(Africa «Africa South of the Sahara» OR «Africa, Western» OR «Africa, Southern» OR «Africa, Northern» OR «Africa, Eastern» OR «Africa, Central» OR Angola OR Benin OR Botswana OR «Burkina Faso» OR «Upper Volta» OR Burundi OR Urundi OR Cameroon OR Cameroons OR «Cape Verde» OR «Central African Republic» OR Chad OR Comoros OR Comoro Islands OR Comores OR Mayotte OR Congo OR Zaire OR «Cote d'Ivoire» OR «Ivory Coast» OR «Democratic Republic of the Congo» OR Djibouti OR «French Somaliland» OR Eritrea OR Ethiopia OR Gabon OR «Gabonese Republic» OR Gambia OR Ghana OR «Gold Coast» OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR «Malagasy Republic» OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR

Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Seychelles OR Senegal OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR «Togolese Republic» OR Uganda OR Zambia OR Zimbabwe OR Rhodesia OR Algeria OR Egypt OR Lybia OR Morocco OR Tunisia OR «Western Sahara»)

#P4 #P1 AND #P2 AND #P3

#P5 Without time restriction

AJOL

#E1 (gout OR «uric acid» OR uricemia OR hyperuricemia OR «crystal, arthropathy» OR tophus OR tophi)

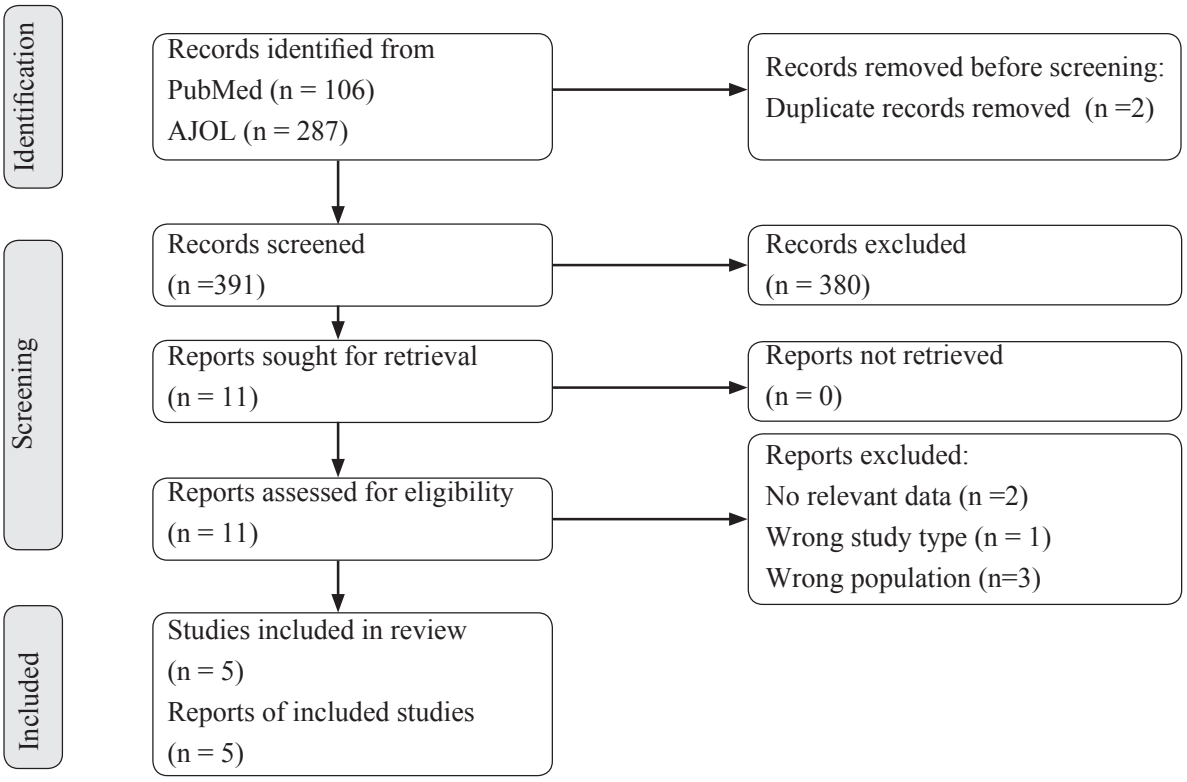
#E2 (genetic OR gene OR genotype OR allele OR genome OR mutation OR polymorphism)

#E3 (Africa OR «Africa South of the Sahara» OR «Africa, Western» OR «Africa, Southern» OR «Africa, Northern» OR «Africa, Eastern» OR «Africa, Central» OR Angola OR Benin OR Botswana OR «Burkina Faso» OR «Upper Volta» OR Burundi OR Urundi OR Cameroon OR Cameroons OR «Cape Verde» OR «Central African Republic» OR Chad OR Comoros OR Comoro Islands OR Comores OR Mayotte OR Congo OR Zaire OR «Cote d'Ivoire» OR «Ivory Coast» OR «Democratic Republic of the Congo» OR Djibouti OR «French Somaliland» OR Eritrea OR Ethiopia OR Gabon OR «Gabonese Republic» OR Gambia OR Ghana OR «Gold Coast» OR Guinea OR Kenya OR Lesotho OR Basutoland OR Liberia OR Madagascar OR «Malagasy Republic» OR Malawi OR Nyasaland OR Mali OR Mauritania OR Mauritius OR Mozambique OR Namibia OR Niger OR Nigeria OR Rwanda OR Sao Tome OR Seychelles OR Senegal OR Sierra Leone OR Somalia OR South Africa OR Sudan OR Swaziland OR Tanzania OR Togo OR «Togolese Republic» OR Uganda OR Zambia OR Zimbabwe OR Rhodesia OR Algeria OR Egypt OR Lybia OR Morocco OR Tunisia OR «Western Sahara»)

#E4 #E1 AND #E2 AND #E3

Search conducted on the 22/02/2024

Figure 1: Flow chart



We included 05 articles, of which 03 were case-control studies, 01 cohort study and 01 case report. The publications came from South Africa (2), Cameroon (1), Mauritus (1) and Tunisia (1). The data extracted from the original studies are summarized in Table 1. With regard to the original articles, two studies focused on genes in gout patients. Cassim *et al*[7] in 1994 in South Africa assessed the association of HLA type 1 (A, B, C) and type 2 (DR, DQ) genes and gout by comparing their frequencies between a group of 46 individuals with gout (including 23 primary and 23 secondary gout) and 2366 gout-free individuals. They found a significant association between the presence of the A28, B14, B70, Cw1, DR8 and DQw3 alleles and primary gout, and the A28 and Cw3 alleles and secondary gout[7]. Nkeck *et al*[8] in 2018 in Cameroon evaluated the association between two non-synonymous variants of the SLC2A9 genes (rs2280205, rs2276961) and gout, by comparing the frequencies of their mutations between 30 patients diagnosed with gout and 30 gout-free controls. They found no significant association. We also found the study by Cummings *et al*[9] in Mauritus in 2010, which assessed the association between uricemia and 97 SNPs of the SLC2A9 gene in a family cohort of 399 members. They found an association between several variants (rs6449213, rs6855911, rs7442295, rs16890979, rs938554 and rs938552) and serum uric acid levels. Finally, Khaliq *et al*[10] in 2020 in South Africa assessed the association between polymorphism of 03 uric acid genes (SLC2A9 (rs1014290), URAT1 (rs505802), PDZK1 (rs12129861) and ABCG2 (rs2231142)) and pre-eclampsia. They analysed data on women who had early preeclampsia (187) or late preeclampsia (170) compared with pregnant women who were not affected (280), and found a significant association between two genes, URAT1 (rs505802) and early preeclampsia, and SLC2A9 (rs1014290) and late preeclampsia. The case report was the study of Rebai et *al*[11] in 2014 which reported a novel mutation in the HPRT1 gene at exon 4 (c.320_326delATGACCAinsCTTTTTTAT) responsible for hypoxanthine-guanine phosphoribosyltransferase deficiency giving rise to Lesch Nyhan syndrome, which is rare a genetic cause of primary gout.

Table 1: Summary of data extracted for included studies

Authors	Year of publication	Country	Objective	Study design	Type of sampling	Prospective /retrospective	Community /hospital-based	Urban/semi-urban/rural	Population or cases	Mean age	Age range	Age group	% males	Control group	Gene(s) studied (Alleles or SNP)	Subgroup (cases)	Allele(s) or SNP associated
Cassim *et al*[7]	1994	South Africa	Association between HLA genes with gout	Case-control	NR	Prospective	Hospital-based	Urban	Gout diagnosed according ARA criteria for gout 1977 (n=46)	NR	NR	Adults	NR	Blood donors and medical staff without gout, no matching details (n=2366)	HLA genes (A, B, C, DR, DQ)	Primary gout (n=23)	A28 B14 B70 Cw1 DR8 DQw3
																Secondary gout (n=23)	A28 Cw3
Cummings *et al*[9]	2010	Mauritus	Association between serum urate level and 97 SNP of SLC2A9	Cohort study	Unclear	NR	Community-based	NR	Mauritian family (399)	50.3	NR	Adults	45.5	NA	SLC2A9 (97 SNP)	NA	rs6449213 rs6855911 rs7442295 rs16890979 rs938554 rs938552
Nkeck *et al*[8]	2018	Cameroon	Association between 2 SNP of SLC2A9 and gout	Case-control	Probabilistic	Prospective	Hospital-based	Urban	Gout diagnosed according ARA criteria for gout 1977 (n=30)	58	NR	Adults	93.3	Healthy individuals without gout, with a normal uricemia paired by age and sex (n=30)	SLC2A9 (2 SNP: rs2280205, rs2276961)	None	None
Khaliq *et al*[10]	2020	South Africa	Association between uric acid gene polymorphism and PE in South African pregnant women with African ancestry	Case -control	Probabilistic	Retrospective	Hospital-based	Urban	Women with EOPE (187)	29.76	NR	Adults	0	Pregnant women without pre-eclampsia (n=280)	SLC2A9 (rs1014290), URAT1 (rs505802), PDZK1 (rs12129861), ABCG2 (rs2231142)	None	URAT1 (rs505802)
									Women with LOPE (170)	27.29	NR	Adults	0			None	SLC2A9 (rs1014290)

NA: Not Applicable; NR: Not Reported; ARA: America Rheumatism Association; PE: Pre-Eclampsia; EOPE: Early Onset Pre-Eclampsia, <33 weeks + 6 days of gestation; LOPE: Late Onset Pre-Eclampsia, >34 weeks of gestation;

*Pre-eclampsia diagnosis: new-onset hypertension (systolic blood pressure ≥140 mmHg and or diastolic blood pressure of ≥90 mmHg) with or without proteinuria (300 mg in a 24-hour quantitative urine test or at least 1+ on a urinary dipstick test).

At the moment, little has been done on genetic studies of uric acid and gout in Africa, and more remains to be known. This is true both for hyperuricaemia and gout, and for uric acid in relation to other medical conditions. Current studies provide a basis for genetic knowledge in the African context, but better knowledge of the genes associated with hyperuricemia and gout will provide a better understanding of the genetic profile and enable us to anticipate the personalized therapies that will become increasingly important in the management of these conditions[12]. In addition, a better genetic understanding of how uricemia is regulated will improve our understanding of the many effects of uric acid in the body, particularly given the genetic diversity of the population on the African continent. We therefore call for more genetic research and publications on uric acid and uric acid-related diseases in Africa. This year 2024, the African Society of Rheumatology ("Société Africaine de Rhumatologie") will hold its 3rd congress, which will be held in Senegal with the main theme of genetics in rheumatology. This will be an opportunity for African researchers to discuss and organize themselves to better shape the future of genetic research in rheumatology in Africa in general and more specifically gout, hyperuricemia and related diseases.

Key words*:* Africa, Genetic, Uric acid, Gout

Declaration

Ethical approval and consent to participate: Not applicable

Consent for publication: Not applicable.

Availability of data and materials: All the dataset generated from this study are available from the corresponding author on request.

Competing interest: The authors declare that they have no competing interests.

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