Received: 20 August 2020 | Accepted: 12 October 2020

DOI: 10.1111/jth.15137

BRIEF REPORT

c.451dupT in *KLKB1* is common in Nigerians, confirming a higher prevalence of severe prekallikrein deficiency in Africans compared to Europeans

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Abstract

Background: Severe prekallikrein deficiency (PK deficiency) is an autosomal-recessive condition thought to be very rare. Recently we reported that the previously unnoticed variant c.451dupT, p.Ser151Phefs*34 in *KLKB1*, which is listed in databases aggregating genome data, causes PK deficiency and is common in Africans according to gnomAD (allele frequency 1.43%).

Patients/Methods: The most common African (c.451dupT) and European (c.1643G>A, p.Cys548Tyr) PK deficiency causing *KLKB1* variants were analyzed in two population-based collectives of 300 Nigerian and 300 German subjects. Genome databases were evaluated for variant frequencies and ethnicity of the subjects. The geographic origin of PK-deficient cases due to 451dupT was assessed.

Results: Two of five patients with PK deficiency caused by homozygous 451dupT were African, one African American, one from Oman, and one of unknown origin. The frequency of 451dupT was 1.17% in the Nigerian collective (7/600 alleles); none had Cys548Tyr. Subjects with 451dupT were found among different Nigerian ethnicities. Both variants were absent in the European collective. Database research was compatible with these findings, even though mainly data of African Americans (451dupT: 1.12%-1.78%) was accessible. A relevant number of non-American Africans are included only in the 1000Genomes collective: 451dupT frequency was 1.29% in native Africans and 1.56% in African Caribbeans.

Conclusions: This study underlines the higher prevalence of PK deficiency among people with African descent compared to Europeans. In order to avoid delay of necessary surgical procedures in patients of African origin, diagnostic algorithms for

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Manuscript handled by: Marcel Levi

Final decision: Marcel Levi, 12 October 2020

Bern, Switzerland

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Funding information
Bundesministerium für Bildung und Forschung, Grant/Award Number: BMBF 01EO1003 and BMBF 01EO1503

isolated, unexplained, activated partial thromboplastin time prolongation in these subjects should include PK deficiency screening.

KEYWORDS
blood coagulation factors, blood coagulation tests, epidemiology, prekallikrein deficiency, prevalence

1 | INTRODUCTION

Isolated prolongation of the activated partial thromboplastin time (aPTT) is a common finding.[1] Adequate and timely differential diagnostic work-up needs to exclude the presence of a bleeding disorder, especially if an invasive procedure is planned. The presence of specific symptoms may orient the diagnostic workup, which includes the identification of pre-analytical issues, the search of coagulation factor deficiencies or coagulation factor inhibitors, and detection of lupus anticoagulant. The local availability of rapid diagnostic assays depends on the severity of the condition being suspected, its expected prevalence, and whether the test is expensive or technically demanding. Severe plasma prekallikrein (PK) and high molecular weight kininogen (HK) deficiency, two autosomal recessive defects of the contact pathway without bleeding diathesis, are considered rare conditions. Therefore, no specific assays are established in many diagnostic laboratories.

We recently performed a large, comprehensive study of all cases of severe PK deficiency discovered thus far, including an appraisal of mutations in the *KLKB1* gene and a bioinformatics analysis to estimate its prevalence.[2] The results suggested very low prevalence of PK deficiency in European collectives, ie, ~1/240 000.[2,3] The internationally so far unnoticed *KLKB1* variant c.451dupT, p.Ser151Phefs*34, which is listed in databases aggregating genome data and had been associated with PK deficiency only in two German-language publications,[4,5] exhibited a much higher frequency in the African (allele frequency according to gnomAD 1.43%) compared to the European collective (0.03%).[2,3] Based on functional and genetic analyses of two native African index cases from our center, we were able to show that homozygosity for 451dupT causes PK deficiency and is associated with non-measurable PK antigen. These data suggest a much higher prevalence of severe PK deficiency in Africans (~1/4725).[2]

Confirming this information may have clinical consequences for the diagnostic workup of patients of African descent with an isolated prolongation of aPTT, allowing a prompt diagnosis of largely asymptomatic PK deficiency. In this study, we analyzed the frequency of 451dupT and Cys548Tyr in *KLKB1* in an African and a European population-based collective to support prevalence estimates of this condition in relation to ethnic and geographic background and to the information available in additional relevant variant databases.

Essentials

- Prekallikrein (PK) deficiency is a recessive trait with isolated aPTT prolongation.
- *KLKB1* c.451dupT is common in Nigerians (7/600 alleles) and absent in a European group (0/600).
- To date, all genotyped PK-deficient patients of African ancestry were homozygous for 451dupT.
- Diagnostics of isolated aPTT prolongation in African descendants should include PK testing.

2 | METHODS

Previously, we showed that 451dupT may represent the main causal variant in subjects of African descent (frequency 1.43%), whereas Cys548Tyr is the main variant in Europeans and Latinos (both 0.1%).[2] All other PK deficiency–causing variants were very rare (≤0.03%) and described in one to a maximum of three index patients.[2] In addition to the patients described in Barco et al,[2] a further patient with PK deficiency originating from Oman, whose case had already been published (case 6 from Nazir and Pathare[6]), was genotyped in our laboratory (University Medical Center of the Johannes Gutenberg University Mainz) for *KLKB1* variants.

Detailed protocols and primer sequences for Sanger sequencing of *KLKB1*, and pyrosequencing of Cys548Tyr are given in Barco et al.[2] The same pyrosequencing procedure was applied for 451dupT using specific primers (forward: AAGGTGCACCAGTAACATTCG, reverse: Bio-CCTTGAATTGTACTCACCGGTACT; sequencing primer: CATTCGCTGCCAGTTTTTTT) and an adequate annealing temperature (56°C).

To substantiate the hypothesis of a higher PK deficiency prevalence in people of African descent than in Caucasians gained from these individual case observations, 300 healthy Nigerian and 300 healthy German subjects were analyzed for the two most common PK deficiency–causing variants in *KLKB1*: c.451dupT, p.Ser151Phefs*34 (rs560588447) and c.1643G>A, p.Cys548Tyr (rs121964951). EDTA blood samples of Nigerian subjects were collected at the Department of Medical Laboratory Sciences, College of Medicine, University of Nigeria in Enugu for a population-based study (Enugu State Ministry of Health [MH/MSD/EC/0194; 01.2019-03.2020]). EDTA blood of German subjects (299 of European, 1 of Asian descent) was obtained between April and July 2019 from consecutive participants of the Gutenberg Health Study, a population-based, prospective, single-center cohort study enrolling participants from the German Rhine-Main area.[7] The studies were designed and executed in accordance with all local legal and regulatory requirements, notably the Declaration of Helsinki, 7th revision.

We accessed the following genetic databases for *KLKB1* variants: (i) dbSNP (build 154), ClinVar, OMIM, Nucleotide, Protein, etc: National Center for Biotechnology Information (NCBI) databases, https://www.ncbi.nlm.nih.gov/; (ii) gnomAD[3]: http://gnomad.broadinstitute.org/; (iii) NCBI ALFA (Allele Frequency Aggregator) project[8]: https://www.ncbi.nlm.nih.gov/snp/docs/gsr/alfa/; (iv) National Heart, Lung, and Blood Institute (NHLBI) GO Exome Sequencing Project (ESP)[9]: https://esp.gs.washington.edu/drupal/; (v) 1000Genomes project, phase 3[10]: https://www.ncbi.nlm.nih.gov/variation/tools/1000genomes/.

The lower and upper limits of the 95% confidence interval (95%CI) for population-based allele frequencies was calculated according to Wilson et al[11] using the web tool http://vassarstats.net/prop1.html.

3 | RESULTS AND DISCUSSION

We started the current project based on the fact that no German patient with PK deficiency has been diagnosed at the University Medical Center Mainz during the past 5 years, but two African-born patients were observed, and although they have a different ethnic background, both were homozygous for 451dupT.[2] One of the recently published PK deficiency cases from Oman[6] has now been analyzed for *KLKB1* variants at our center in Mainz. A homozygosity for 451dupT was detected. Together with a recently published report[12] about a case homozygous for 451dupT, and two cases, which had already been part of a case summary in Barco et al,2 a total of six PK deficiency cases carrying 451dupT are known to date, five of them being homozygous and one compound heterozygous (Table 1). Two homozygous patients originated from Africa (Ghana and Somalia; Figure 1 and Table 1). One homozygous patient is African American (personal communication with Thiagarajan P.[12]; Table 1). The ethnicity of a further homozygous[2,4] and a compound heterozygous case[2,5] is unknown.

The mutation Cys548Tyr was described in 11 of 28 genotyped index patients, of whom 5 were homozygotes and 6 compound heterozygotes.[2] The majority of these patients with known ethnicity were European (5 Europeans, 1 of Afro-Caribbean origin, 5 of unknown origin).

Pyrosequencing of 300 Nigerian individuals revealed seven heterozygotes for 451dupT (Figure 1) corresponding to an allele frequency of 1.17%. Cys548Tyr was not detected. Subjects with one 451dupT allele were found among different Nigerian ethnicities: four Ibo/Igbo, one Idoma, one Ibibio, and one Urhobo. Figure 1 describes the geographic and ethnic distribution of 451dupT in Nigeria and, based on this and prior reports,[2,6] in the African and Middle-East region.

TABLE 1 All published cases and one newly identified subject with PK deficiency, that is caused by either homozygous or compound heterozygous 451dupT variant are listed in the table. The region of origin of the three PK-deficient patients with ethnic information (Oman, Ghana, and Somalia) are highlighted in blue for easy comparison with Figure 1

Reference	Case	Ethnicity	Allele 1	Allele 2	PK:C (%)	PK:Ag (%)
This study (case 6 from Nazir[6])	34, F (case 88-3[2])	Oman	c.451dupT, p.Ser151Phefs*34	c.451dupT, p.Ser151Phefs*34	6	NA
Barco[2]	68, F (case 1[2])	Ghana	c.451dupT, p.Ser151Phefs*34	c.451dupT, p.Ser151Phefs*34	<1	<1
Barco[2]	26, M (case 3[2])	Somalia	c.451dupT, p.Ser151Phefs*34	c.451dupT, p.Ser151Phefs*34	<1	<1
Dasgupta[12]	67, M	African American°	c.451dupT, p.Ser151Phefs*34	c.451dupT, p.Ser151Phefs*34	<1	NA
Farac[4]	34, F (case 9-1[2])	NA	c.451dupT, p.Ser151Phefs*34	c.451dupT, p.Ser151Phefs*34	NA	NA
Maak[5]	14, M (case 23-1[2])	NA	c.451dupT, p.Ser151Phefs*34	c.1643G>A, p.Cys548Tyr	<1	NA

Note: °= personal communication with Thiagarajan P.[12];

Abbreviations; NA, not available; PK, prekallikrein; PK:Ag, prekallikrein antigen; PK:C, prekallikrein clotting activity.

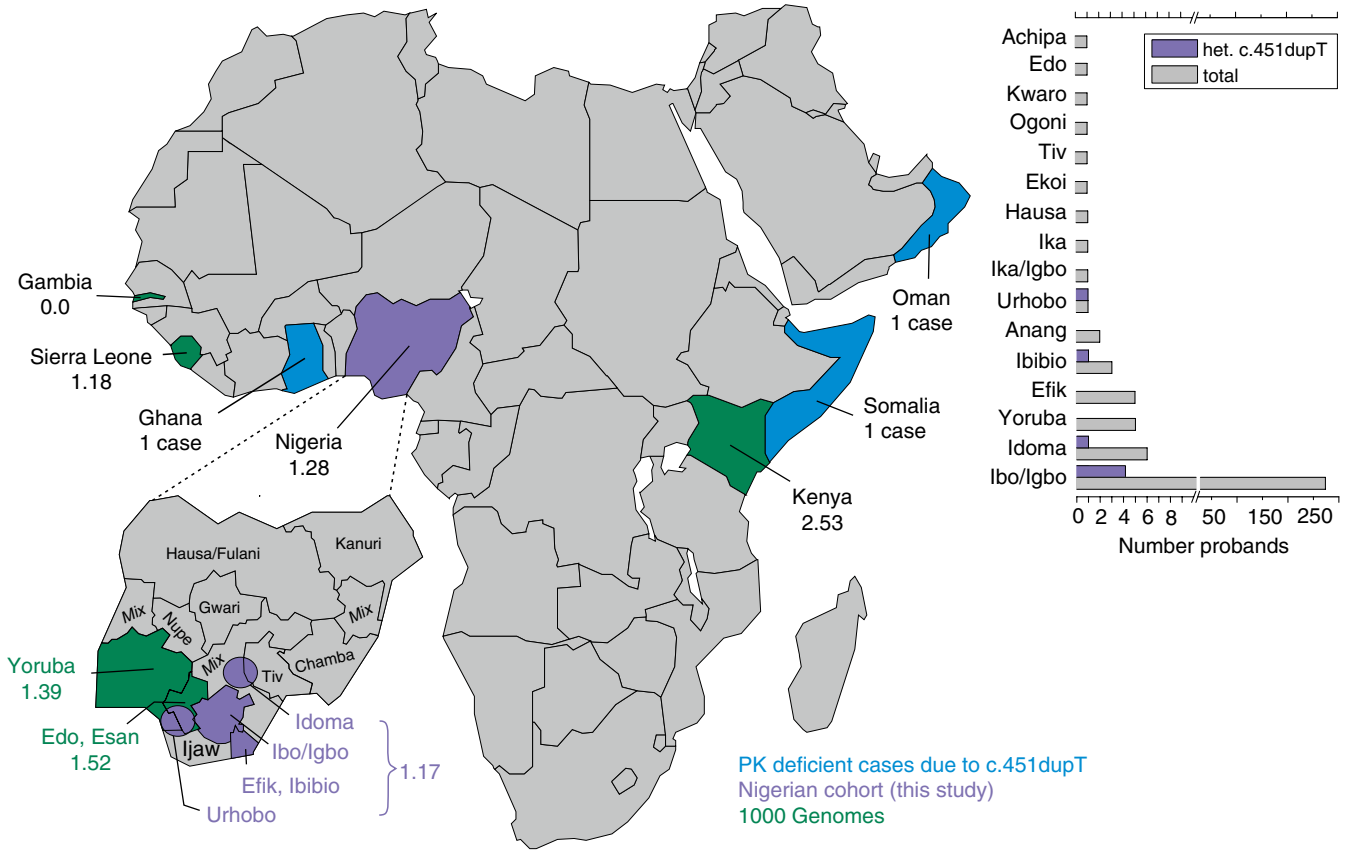

FIGURE 1 Schematic representation of Africa and the Arabian Peninsula to illustrate the broad distribution of *KLKB1* c.451dupT in this region. Settlement areas of different ethnic groups from Nigeria, analyzed in this report, are shown in purple. Cohorts of the 1000Genomes project, which are described in more detail in the text, are marked in dark green. The allele frequencies in percent of 451dupT are given below the respective region. Mix = Igbira, Borim, Bauchi, Margi, Idoma, Ekoi, Igala; het = heterozygous

451dupT and Cys548Tyr were both absent from the European collective of 300, mainly German subjects, a finding consistent with the rarity of PK deficiency in Europe. The reason more Europeans than Africans have been identified with PK deficiency in the past is presumably due to the frequency of aPTT testing and the higher availability of detailed investigations to study prolonged aPTT in Europe.

A more detailed analysis of selected databases revealed that 451dupT is not only frequent among Africans, but also among individuals of African descent, including African Americans and African Caribbeans:

1. The database of the **NCBI ALFA project**[8] lists 676 African alleles, 662 of which are African American. In this relatively small sample 451dupT (rs560588447) is found with an allele frequency of 0.60% in African Americans. In a total of 8134 genotyped European alleles the allele frequency of 451dupT is given with 0.04%. For Cys548Tyr (rs121964951) NCBI ALFA reports a minor allele frequency of 0.086% in Europeans (79 462 alleles). The variant is absent in Africans (844 African alleles, including 828 African-American alleles).[8] Interestingly, the clinical significance of 451dupT is categorized as "benign" in the NCBI databases (dbSNP, ClinVar), while the clinical significance of Cys548Tyr is categorized as "uncertain significance" or "pathogenic." Nevertheless, it is obvious that both variants are definitely causing PK deficiency, whereby homozygosity for 451dupT is associated with CRIM (cross reacting immunological material) negativity, while homozygosity or compound heterozygosity for Cys548Tyr is associated with very low PK activity, but some 10% of PK antigen (CRIM+).[2,13] The latter is consistent with the observation of Saito et al,[14] who described a CRIM– status for 13 African Americans and a CRIM+ status for 5 Caucasian individuals, though no genetic data was presented.
2. The **GO Exome Sequencing Project of the NHLBI**[9] presents the largest genotyped collective of individuals of African descent. A frequency of 1.52% is reported for 451dupT in African Americans (4266 alleles) and a frequency of 0.024% in European Americans (8254 alleles). Cys548Tyr, on the other hand, is found with a frequency of 0.047% in European Americans (8594 alleles) and is absent in the African-American collective (4402 alleles).
3. The **1000Genomes project, phase 3**,[10] presents an interesting African collective (consisting of 1322 alleles), which includes African Americans (122 alleles), African Caribbeans (192 alleles), and, in contrast to the other analyzed databases, a significant number of genuine African alleles (1008). The frequency of 451dupT was 1.36% in the entire African collective, with a frequency of

TABLE 2 Summary of frequency data for 451dupT in African collectives, compiled from genome databases and compared to the allele frequencies determined in this study

	Data source	Ethnicity	Total allele count	c.451dupT alleles	MAF (%)	95% confidence interval
African descent	ALFA	African Americans	662	4	0.60	
	GO Exome sequencing	African Americans	4266	65	1.52	
	1000Genomes	African Americans	122	2	1.64	
	1000Genomes	African Carribeans	192	3	1.56	
	All of African descent (native Africans excluded)		5242	74	1.41	1.12-1.78
Native Africans	This study	Nigerians	600	7	1.17	0.51-2.50
	1000Genomes	Kenyans, Gambians, Nigerians, Sierra Leoneans	1008	13	1.29	
	All native Africans		1608	20	1.24	0.78-1.95

Abbreviation: MAF, minor allele frequency.

1.64% in African Americans, 1.56% in African Caribbeans, and 1.29% in native Africans. The detailed frequency distribution in the African sub-collectives from Gambia (226 alleles), Sierra Leone (170), Nigeria (ethnicities: Yoruba, 216 alleles and Esan, 198 alleles]), and Kenya (Luhya, 198 alleles) is given in Figure 1. These data, as well as our Nigerian collective (ethnicity mainly Igbo), confirm the broad distribution of 451dupT in African collectives, although 451dupT was not found in Gambia among 226 alleles. Cys548Tyr was absent from the African and the European (1006 alleles) collective in 1000Genomes.

Although our data, as well as database research, suggest that 451dupT is widely distributed among Africans and individuals of African descent (Figure 1, Table 1), further studies are needed to expand the dataset and identify regional differences in more detail.

Whether the frequency of 451dupT in African collectives is caused by a heterozygote advantage currently remains speculative. Several components of the kinin system, including kallikrein, play a major role in a series of infectious conditions, such as malaria.[15] Infectious diseases, especially if they are life threatening, can exert a strong selection pressure on a population and might cause an advantage for 451dupT heterozygotes.

In summary, according to the collectives studied to date, the frequency of 451dupT, a PK deficiency–causing *KLKB1* variant, is 1.24% (95%CI: 0.78%-1.95%) in native Africans and not significantly different in populations of African descent, including African Americans and African Caribbeans (Table 2). This indicates that PK deficiency, which is rare in individuals of European origin (PK deficiency–causing variant Cys548Tyr: 0.1%; the four next most common variants 0.01%-0.03%, additionally several private variants; estimated prevalence of PK deficiency ~ 1:240 000[2]), is much more frequent in most African communities. As no further PK deficiency–causing variants have been identified in Africans to date, a rough estimation of PK deficiency prevalence from the allele frequency of 451dupT (1.17%, 95%CI: see Table 2) is possible. Our results suggest a PK deficiency prevalence of about 1:7000 for Nigeria. Assuming a population of about 206 million, we expect almost 30 000 individuals with PK deficiency in Nigeria. So, in a Nigerian laboratory of the size of our laboratory in Mainz with about 600 aPTT measurements per day, one aPTT prolongation due to PK deficiency can be expected every 12 days.

Of note, approximately 13% of the U.S. population is of African descent,[16] 200 million in the Americas,[17] and 15 million in the European Union,[18] making this a relevant issue not only in Africa, which currently has a population of about 1.3 billion people.[19] Based on these figures, and the allele frequencies for c.451dupT given in Table 2, one could conservatively estimate that 200 000 people worldwide might have severe PK deficiency.

Nevertheless, due to the supposed rarity of PK deficiency, the vast majority of laboratories do not perform an assay for PK activity. In order to avoid unnecessary delay of surgical procedures in Africans or people of African descent with prolonged aPTT, we recommend to establish (a) a functional assay to assess PK activity, (b) an assay documenting the normalization of aPTT following increased pre-incubation time,[20] or (c) a simple single nucleotide polymorphism assay to confirm the presence of 451dupT.

We would nevertheless like to emphasize that testing for clinically relevant causes of prolonged aPTT has priority. If PK- and HK-deficient plasmas are available, a laboratory capable of measuring other coagulation factors based on a modified aPTT test should also be able to measure PK and HK activity in time, because the techniques are the same.

ACKNOWLEDGMENTS

The research project has been carried out at the University Medical Center of the Johannes Gutenberg University (Mainz, Germany) and was not funded. The work of A. Adenaeuer, S. Barco, K. Lackner, B. Lämmle, and H. Rossmann (platform "Advanced Diagnostics," Center for Thrombosis and Hemostasis) is supported by the German Federal Ministry of Education and Research (BMBF 01EO1003

and 01EO1503). Open access funding is enabled and organized by Projekt DEAL. Open access funding enabled and organized by ProjektDEAL.

CONFLICTS OF INTEREST

None of the authors reports any conflict of interest with the present work.

AUTHOR CONTRIBUTIONS

Concept and design of the study, and writing of the manuscript: A. Adenaeuer, S. Barco, K. Lackner, B. Lämmle, H. Rossmann. Acquisition and interpretation of data: A. Adenaeuer, E. Ezigbo, H. Nazir, S. Barco, A. Trinchero, D. Laubert-Reh, P. Wild, B. Lämmle, H. Rossmann. Laboratory and bioinformatics analysis: A. Adenaeuer, E. Ezigbo, H. Nazir, D. Laubert-Reh, K. Strauch, P. Wild, H. Rossmann. Critical revision for important intellectual content and final approval: A. Adenaeuer, E. Ezigbo, H. Nazir, S. Barco, A. Trinchero, D. Laubert-Reh, K. Strauch, P. Wild, K. Lackner, B. Lämmle, H. Rossmann.

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How to cite this article: Adenaeuer A, Ezigbo ED, Fawzy Nazir H, et al. c.451dupT in *KLKB1* is common in Nigerians, confirming a higher prevalence of severe prekallikrein deficiency in Africans compared to Europeans. *J Thromb Haemost*. 2021;19:147–152. https://doi.org/10.1111/jth.15137