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ORIGINAL ARTICLE

An exploration of the genetics of the mutant *Huntingtin* (*mHtt*) gene in a cohort of patients with chorea from different ethnic groups in sub-Saharan Africa

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Abstract

Background: Africans are underrepresented in Huntington's disease (HD) research. A European ancestor was postulated to have introduced the mutant *Huntingtin* (*mHtt*) gene to the continent; however, recent work has shown the existence of a unique *Htt* haplotype in South-Africa specific to indigenous Africans.

Objective: We aimed to investigate the CAG trinucleotide repeats expansion in the *Htt* gene in a geographically diverse cohort of patients with chorea and unaffected controls from sub-Saharan Africa.

Methods: We evaluated 99 participants: 43 patients with chorea, 21 asymptomatic first-degree relatives of subjects with chorea, and 35 healthy controls for the presence of the *mHtt*. Participants were recruited from 5 African countries. Additional data were collected from patients positive for the *mHtt* gene; these included demographics, the presence of psychiatric and (or) cognitive symptoms, family history, spoken languages, and ethnic origin. Additionally, their pedigrees

were examined to estimate the number of people at risk of developing HD and to trace back the earliest account of the disease in each region.

Results: HD cases were identified in all countries. Overall, 53.4% of patients with chorea were carriers for the *mHTT*; median tract size was 45 CAG repeats. Of the asymptomatic relatives, 28.6% (6/21) were carriers for the *mHTT;* median tract size was 40 CAG. No homozygous carries were identified. Median CAG tract size in controls was 17 CAG repeats. Men and women were equally affected by HD. All patients with HD—bar three who were juvenile onset of <21 years—were defined as adult onset (median age of onset was 40 years). HD transmission followed an autosomal dominant pattern in 84.2% (16/19) of HD families. In familial cases, maternal transmission was higher 52.6% (10/19) than paternal transmission 36.8% (7/19). The number of asymptomatic individuals at risk of developing HD was estimated at ten times more than the symptomatic patients. HD could be traced back to the early 1900s in most African sites. HD cases spread over seven ethnic groups belonging to two distinct linguistic lineages separated from each other approximately 54–16 kya ago: Nilo-Sahara and Niger-Congo.

Conclusion: This is the first study examining HD in multiple sites in sub-Saharan Africa. We demonstrated that HD is found in multiple ethnic groups residing in five sub-Saharan African countries including the first genetically confirmed HD cases from Guinea and Kenya. The prevalence of HD in the African continent, its associated socio-economic impact, and genetic origins need further exploration and reappraisal.

KEYWORDS
Huntington disease, *mHTT*, Niger-Congo, sub-Saharan African origin

1 | INTRODUCTION

Huntington's disease (HD) is an autosomal dominant neurodegenerative condition causing progressive loss of cognition, movement disorder, and psychiatric symptoms (Huntington, 1872). HD results from an expansion of a CAG nucleotides repeat within exon 1 of the *Huntingtin (HTT)* gene (The Huntington Disease Collaborative Research Group, 1993).

Historically, HD was first described by the name "setesdalryyja" in 1860 by the Norwegian neurologist (Lund, 1860). Twelve years later, George S Huntington published his famous assay "On Chorea" in North America, describing the clinical manifestation of the disease in English (Huntington, 1872). Since then, HD cases have been reported in most countries across the globe (Heathfield, 1973; Huntington, 1872, 2003; Okun & Thommi, 2004; Wexler et al., 2016). In Africa, the earliest documented account of HD was in 1936 in a Mugikuyu psychiatric patient from Kenya (Gordon, 1936). In, Scrimgeour (1981) reported a family with several affected individuals with possible affected ancestors that could be traced back to at least two people born in the 1870s, in Tanzania. Elsewhere in Africa, clinical accounts of HD have been reported from Nigeria, Senegal, South Africa, Sudan, Tanzania, Togo, Uganda, and Zimbabwe (Glass & Saffer, 1979; Grunitzky et al., 1995; Hayden et al., 1980; Morakinyo, 1983; Samuels & Gelfand, 1978; Scrimgeour, 1981; Stephany et al., 1984). Genetic testing was used in the reporting of cases positive for *Huntingtin* mutation (*mHTT)* in Burkina Faso, South Africa, Egypt, Morocco, Mali, and the Gambia (Bocoum et al., 2022; Bouhouche et al., 2015; Kabore & Ouedraogo, 2000; Kremer et al., 1994; Magazi et al., 2008; Silber et al., 1998). However, the knowledge about the exact origin and the distribution of *mHTT* in the continent is sparse. A small number of studies traced the origin of the *mHTT* to ethnic groups from South Africa, Tanzania, and Zimbabwe and suggested that the mutation was either introduced by European migrations or originated from native pathogenic variants in the *HTT* gene, as demonstrated by haplotype analyses (Baine et al., 2013; Hayden et al., 1980; Scrimgeour & Pfumojena, 1992; Squitieri et al., 2020; Warby et al., 2011).

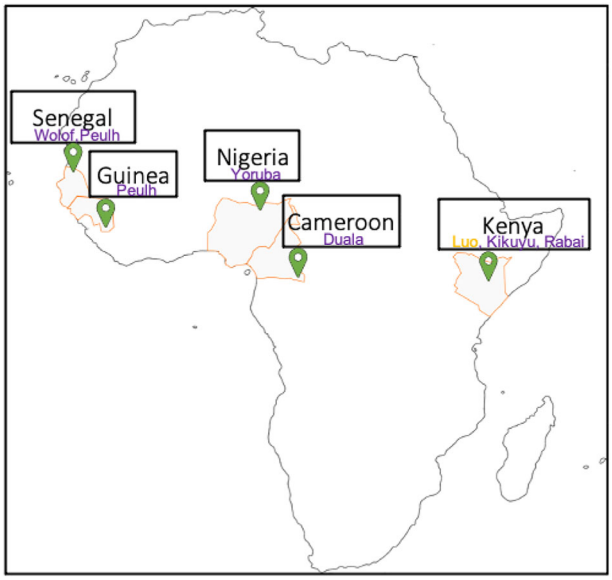


FIGURE 1 Study sites and ethnic origins of Huntington's disease (HD) families. Movement disorders centers in five African countries contributed to this cohort namely Kenya, Cameroon, Nigeria, Senegal and Guinea. In total 19 HD families from 7 ethnic groups were identified. These ethnic groups belong to two ethnolinguistic origins—a Niger-Congo (purple) and Nilo-Saharan (yellow). The names of the seven ethnic groups (purple and yellow) are listed in the map above according to their locations/countries of origin.

Novel therapeutic approaches targeting the *mHTT* are currently in clinical trial (Estevez-Fraga et al., 2020; Kumar et al., 2020). Addressing gaps in knowledge about HD among sub-Saharan Africans is needed if people of this ethnic origin are to benefit from developing novel therapies. To achieve this objective, we formed a consortium—the African Research Consortium on Huntington's disease (ARCH)—comprising of predominantly early career African academics and movement disorders specialists whose focus is studying HD in the continent. We aim to characterize genetically and phenotypically a geographically diverse cohort of cases of HD from sub-Saharan Africa. Here, we report on ARCH's first cohort study from five African countries.

2 | MATERIALS AND METHODS

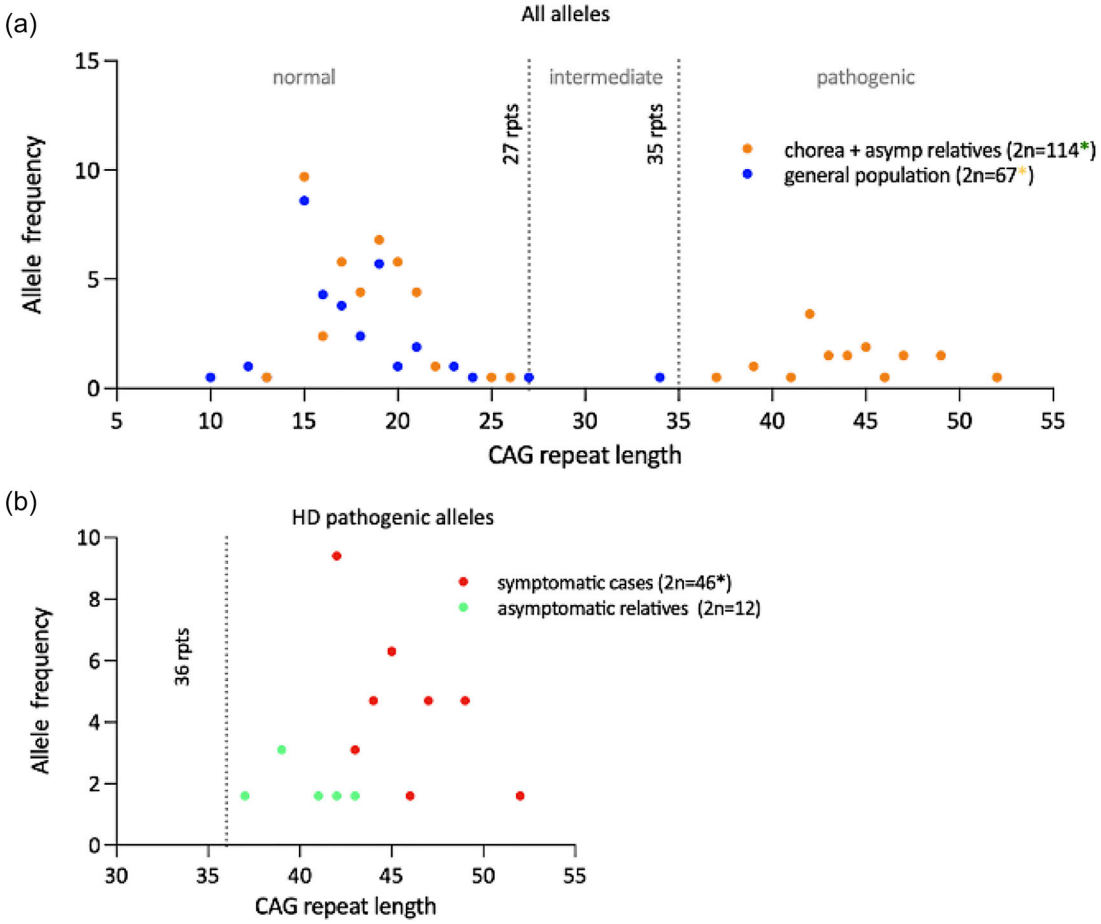
Patients with chorea and their first-degree relatives were recruited from movement disorder clinics in five African countries: Cameroon, Guinea, Kenya, Nigeria, and Senegal, between January 2020 and October 2021 (Figure 1). Cases were identified from medical records at the participating centers. Healthy individuals without a neurological illness or a family history of a neurological illness from the same populations were included as controls. Participant selection and assessments were performed by movement disorders specialists authoring this manuscript.

Ethical approvals were obtained from the institutional research ethics boards of the participating institutions. Details as follow: the University College London and the National Hospital for Neurology and Neurosurgery, London, UK, Ref: 07/Q0512/26, University Hospital Center of Conakry, Guinea: Ref: 353/CE HNID/CHU/CONAKRY/2020, Centre Hospitalier National de Pikine, Service de Neurologie, Dakar, Senegal: Ref: 00000087/MSAS/CNERS/SP du 14 June 2021, Department of Medicine, Aga Khan University Medical College of East Africa, Nairobi, Kenya Ref:2020/IERC-108 and NACOSTI/P/20/7553. For three families, two from Nigeria and one from Cameroon; informed consent was obtained by the principal investigator clinicians. All participants gave their written consent at each study site according to the Declaration of Helsinki and The Common Rule. For individuals deemed to lack capacity to consent, study sites applied country-specific guidelines for signing consent forms.

DNA was isolated from either EDTA-blood or buccal swabs or saliva. Fragments analysis using a PCR method followed by capillary electrophoresis was applied to estimate the CAG tract size in exon 1 of the *HTT* gene, as previously described (Potter et al., 2004). All samples except those from Kenya were genotyped at UCL Queen Square Institute of Neurology, London, UK. The Kenyan samples were genotyped either commercially or in-house at the Aga Khan University Hospital in Nairobi.

Additional data from individuals with the *mHTT* (CAG tract >35) were collected; this included gender, any behavioral, psychiatric, and cognitive symptoms, age at experiencing the first neurological or behavioral and psychiatric manifestations, family history, spoken language, and ethnic origin.

Genealogical analysis was performed by examining at least three generations for each individual's family to acquire sufficient information on consanguinity, number of individuals in each generation, number of individuals with possible HD symptoms, and the age when symptoms were experienced, and age at death (if deceased). Whenever possible, family trees were extended back to the fourth and fifth generations to trace back the oldest known individuals with HD symptoms. Additionally, pedigrees were examined to estimate the transmission pattern (i.e., maternal or paternal) of the *mHTT* and the total number of living persons at risk of developing HD. Data analysis was performed using Microsoft Excel or GraphPad Prism Version 8.0.



(c)

	General Population	HD cases & asymptomatic carriers	
Allele name (Range CAG length)	**Control *mHTT* -ve**	**Symptomatic *mHTT* +ve**	**Asymptomatic *mHTT* +ve**
Normal allele (≤27)	17.0 , (10—24)[1,*]	17.3 , (13—21)[3,*]	19.0 , (15—21)[5]
Intermediate allele (27—35)	30.5 , (27—34)[2]	na	
Reduced penetrance (36 —39)	na	na	39.0 , (37—39)[6]
Complete penetrance (≥40)	na	45.0 , (42—52)[4]	40.0 , (37—43)[7]

FIGURE 2 Allele frequency distribution: (a) allele frequencies of CAG repeats in all 99 participants (i.e., 43 patients, 21 asymptomatic relatives, and 35 controls). CAG tracts are categorized as normal (wild type), intermediate or pathogenic. Allele dropouts due to PCR failure are denoted as asterisks (ADO): Amber asterisk = 3 alleles and green asterisk = 14 alleles; (b) allele frequencies of expanded-pathogenic CAG repeats (>35), in patients and asymptomatic relatives who are positive for the Huntington's disease (HD) gene. ADO denoted as black asterisk = 2; (c) alleles' classification for controls, patients, and asymptomatic carriers. Superscripts represent the number of alleles where: [1]($2n = 64$), *(3 ADO); [2]($n = 2$); [3]($n = 21$), *(2 ADO); [4]($n = 23$); [5]($n = 6$); [6]($n = 3$); and [7]($n = 3$).

3 | RESULTS

CAG tract sizes were determined from 99 participants: 43 patients with chorea, 21 asymptomatic first-degree relatives, and 35 unrelated healthy controls. Overall, 181 out of possible 198 alleles were successfully genotyped; 17 alleles dropped out during genotyping due to PCR failure (Figure 2a–c).

The size of the most prevalent wild type allele in all individuals was 15 repeats (cumulatively at 8.6%), and the size of the most prevalent *mHTT* in patients and asymptomatic relatives was 42 repeats (cumulatively at 3.4%). In total, 28 individuals (23 patients and 6 asymptomatic relatives) carried one allele with CAG repeats within the pathogenic range for HD (>35 repeats) (Figure 2a–c). No homozygous carriers were identified.

Overall, 53.4% (23/43) of patients were heterozygous carriers for the *mHTT* allele; with median repeat sizes of 45 (mode 42, range 42–52). Overall, 28.6% (6/21) of the asymptomatic relatives were heterozygous carriers for the *mHTT* allele; with a median repeat size of 40 (mode 39, range 37–43). In controls, the median CAG tract size was 17 (mode 15, range 10–34). Notably, all 23 patients who were carriers of the *mHTT* had expanded CAG repeats within the complete penetrance category of >39 repeats. Intermediate CAG repeats with lengths measuring 27 and 34 were detected only in two healthy controls—one from Guinea and one from Senegal, respectively. The tract sizes and the frequency distributions of the wild-type *HTT* (<27 CAG repeats), intermediate *HTT* (27–35 CAG repeats), and the *mHTT* allele (>35 CAG repeats) in all individuals are summarized in Figure 2a–c.

The 23 patients with the *mHTT* belonged to 19 distinct families that were identified from all the recruitment sites: Cameroon 1 patient (1 family), Guinea 5 patients (5 families), Kenya 5 patients (5 families), Nigeria 4 patients (2 families), and Senegal 8 patients (6 families). Overall, 52.1% (12/23) men and 47.8% (11/23) women were affected by HD. Overall, 78% (18/23) HD patients had cognitive disturbance and 73.9% (17/23) had behavioral and psychiatric symptoms. Overall, 87% (20/23) developed adult-onset HD (age at onset in years: median 40, mode 45, range 23–62). Juvenile onset HD (JHD) affected 13% (3/23) of patients; of these cases, 2 were from Senegal (aged 18 and 20 years) with 46 and 45 CAG repeats, respectively. A single case of a 20-year-old JHD with 49 CAG repeats was identified from Cameroon.

A multigenerational history of HD symptoms was identified in 84.2% (16/19) of the families. Three out of the 19 families were without a multigenerational HD history; one proband from Kenya was a confirmed sporadic case of HD, and in 2 families from Cameroon and Senegal, there was insufficient genealogical data to infer a clear family history of HD. Of the families with a clear multigenerational history of HD, 56% (9/16) had a maternal transmission, whereas 44% (7/16) had a paternal transmission pattern. Overall, 10.5% (2/19) of families had consanguineous marriages: 1 from Guinea and 1 from Senegal.

An additional 15–21 males and 6 females—living individuals were identified as possibly having symptomatic HD in 2–4 generations in the 19 families. A further 198 were estimated to be asymptomatic and at-risk for HD: 105 males, 90 females, and 3 unknowns. Note that at-risk individuals were asymptomatic and of undetermined HD genotype but had shared ancestry with the proband over several generations. Of the 198 persons at risk, 121 were first degree relatives (i.e., parents, offspring or siblings of the proband). The largest number of people at risk were from large families in Guinea, Kenya, and Senegal.

A possible history of HD—based on tracing the oldest HD ancestors with symptoms in the 19 families—was traced back to the 1900s at most sites. In at least one large kindred from Kenya, we have been able to trace accounts of HD to the early 1900: with possible relatives stretching back to the mid-1800s (Supplementary material A).

HD patients were linked to seven genetically unique ethnic groups: Fulani (Peulh), Wolof, and Yoruba from West Africa; the Duala from Central Africa and the Rabai, Kikuyu, and Luo from East Africa (Figure 1). The seven ethnic groups came from 2 distinct ethnolinguistic origin: Niger-Congo lineages included Fulani (Peulh), Wolof, Yoruba, Duala, Rabai, and Kikuyu while the Luo people were from a Nilo-Saharan lineage. Overall, 94.7% (18/19 families) were identified as Niger-Congo and only 5.3% (1/19 families) were identified as Nilo-Saharan (Figure 1). Detailed regional observations of HD patients and their families per country are listed in Supplementary material B.

4 | DISCUSSION

In Kenya, in 2020, the Swahili word "Uku" was designated by Huntington disease Africa (https://hd-africa.org/) to mean HD. In the majority of the local communities in Africa HD is not recognized and it has no name. Internationally, little is known about HD in Africans (Harper, 1992; Krause et al., 2015). Current knowledge comes from a few random case reports and several South African-based genetic studies mainly in people from a mixed ancestry or Bantu-speaking ethnic groups (Baine et al., 2013, 2016; Bouhouche et al., 2015; Kabore & Ouedraogo, 2000; Krause et al., 2015; Magazi et al., 2008; Silber et al., 1998). Here, we report on a cohort of African patients and first-degree relatives with a confirmed genetic diagnosis of HD from seven different ethnic origins spanning five sub-Saharan countries—including the first genetically confirmed HD cases from Guinea and Kenya.

Overall, 53% of patients with chorea in this cohort tested positive for the *mHTT*; this percentage is higher than previously reported in sub-Saharan South Africans (36%), but lower than the reported figures from other populations (Krause et al., 2015). It is plausible that a significant proportion of the 47% of patients in our study who are negative of the *mHTT* do harbor HD phenocopies such as the HD-like syndrome 2, which was reported solely in patients with chorea from sub-Saharan South African populations; further characterization of these HD negative cases is required (Krause et al., 2015).

The *mHTT* tract sizes in our patients and their asymptomatic relatives were similar to the previously reported sizes in both sub-Saharan South Africans (Baine et al., 2013; Krause et al., 2015) and in HD cases in other ethnic groups (Baine et al., 2013); however, several observations from our study—and in line with previous studies—suggest that the *HTT* locus in indigenous sub-Saharan African populations is possibly more stable than in Europeans (Kay et al., 2018). First, the commonest CAG repeat size in our cohort was 15, similar to previous reports in sub-Saharan South Africans, which is less than the average tract sizes in Europeans (18) and Asians (17) (Squitieri et al., 1994; Xu & Wu, 2015). Second, all HD cases in our study had CAG tracts within the full penetrance range (>39 repeats), comparable to reports from sub-Saharan South Africans where 98%–99% of African patients with HD had repeat sizes within full penetrance range (Baine et al., 2013; Krause et al., 2015). Third, in our cohort, the CAG repeats within the reduced penetrance range (36–39 repeats) were only detected in asymptomatic relatives, and none of the controls had alleles within the mutable range.

With few regional variations, most HD patients in our study developed symptoms in their thirties and forties; the eldest patient being 62 years old. Psychiatric and cognitive symptoms were identified in over 70% of HD patients: slightly more than reported in other studies (Vinther-Jensen et al., 2014). Juvenile cases constituted 13% (3/23) of HD patients in our cohort. This figure is similar to the percentage of JHD previously observed in patients from African origin (Squitieri et al., 2020); however, due to the small size of our cohort, it is difficult to draw comparisons between our results and the 4%–10% (average ≈6%) of JHD reported in European and North American cohorts (Quarrell et al., 2012, 2013). To clarify, in this cohort, the term JHD pertains to individuals who manifested symptoms before the age of 21 and does not denote a specific clinical phenotype.

As expected with an autosomal dominant pattern of inheritance, 84% of our families had a multigenerational history of HD symptoms, and ≈29% of the first-degree asymptomatic relatives included in this study were found to be carriers of the *mHTT*. Consanguinity was detected in 10.5% (2/19) of HD families, highlighting the need to explore the role of customary and traditional practices in hereditary rare diseases in these indigenous communities. In familial cases, maternal transmission was higher than paternal transmission (56% and 44%, respectively). No gender differences were observed. Nonetheless, inspection of the family trees of affected individuals showed a higher proportion of males are at risk of carrying the *mHTT* compared to females. The number of individuals identified at risk of developing HD was estimated to be around ten times the number of people tested positive in our study; this raises the possibility of a higher prevalence of HD across sub-Saharan African than currently believed (Harper, 1992; Hayden et al., 1980).

One of the important findings from this cohort is that in one of the Kenyan families, we were able to trace back an ancestor with HD symptoms to the early 1900 (Supplementary material A). This account suggests that the preceding generation of the reported family could be from a similar time point as the previously reported earliest case in the literature by Scrimgeour in 1870s (Scrimgeour, 1981) and is possibly one of the two earliest documented accounts in sub-Saharan Africans. Interestingly, in a recent study, Squitieri et al. (2020) described a distinct African *HTT* haplotype (C6 × C9) in a large family from Oman in the Middle East. The authors were able to trace the ancestors with HD of this family back to the mid-1800s, particularly to the Nyamwezi ethnic group, which is part of the Bantu communities in Southeast Africa. The authors proposed that a unique African pathogenic haplotype was present in affected individuals in this family, and it was passed down through the paternal lineage from Southeast Africa to Oman.

Another important finding from our study is that the patients with *mHTT* allele were widely spread across seven ethnic groups in sub-Saharan Africa—belonging to two genetically distinct ethnolinguistic lineages (the Niger-Congo and Nilo-Sahara), which diverged approximately 54–16 kya ago (Fan et al., 2019)—suggesting that perhaps the present-day ancestors carrying *mHtt* from these lineages had multiple ancestral origins for the CAG expansion mutation. These multiple ancestral origins possibly coincide with migratory routes of modern-day Sub-Saharan Africans. It is worth noting that throughout history, different disease-causing variations of the *HTT* gene have emerged spontaneously and independently in various geographical regions worldwide and have subsequently spread through migration. The analysis of haplotypes allows for the identification of the population from which a *mHTT* originated. In European and Caucasian populations, *HTT* CAG expansions are typically observed on haplogroup A, whereas in populations of sub-Saharan African and East Asian descent, they are more frequently found on specific variants of haplogroups B and C. The recent work by Squitieri et al. (2020) and others (Baine et al., 2013) have shown that specific *HTT* haplotypes originating from Africa can be traced back to sub-Saharan ethnic groups and linked to migratory routes within and outside of Africa. These findings, along with the observation from our study that distinct African ethnic groups separated for over 16,000 years have the *HTT* pathogenic mutation, suggest that the m*HTT* in current sub-Saharan Africans probably predated the modern Europeans migration to Africa and challenge the theory that the

mutation was first brought to the continent by Europeans. Indeed, investigating the *HTT* haplotypes in these 7 distinct ethnic groups is essential to trace the origin of *mHTT* in sub-Saharan Africa.

In conclusion, we have identified sub-Saharan African families with *mHTT* from different ethnic groups across the region. This cohort is the largest group of patients with genetically confirmed HD from different countries in the continent. Our findings call for a revision of the possibly underestimated HD prevalence data in Africa. Further investigation of the genetic variations, haplotypes, and modifiers of HD progression for this cohort is also warranted. We acknowledge the limitations of this study—including the small sample size, the lack of detailed clinical assessment using standardized rating scales for HD patients, which limited our ability to clinically characterize any atypical features, particularly in cases with JHD.

Planned future work from our group includes conducting detailed phenotypic assessments of this cohort using clinical scales and imaging. To better understand the HD locus in Africans, we are planning to assess haplotypes and within tract changes in patients with HD and to investigate HD phenocopies in HD negative cases. In collaboration with Huntington disease Africa (https://hd-africa.org/)—the main HD-patient advocacy group in Africa—our ARCH group aims to build a HD registry featuring patients and asymptomatic relatives from the five African participating countries. We hope this registry will serve as a foundation for epidemiology, clinical, biomarkers, and genetic studies as well as a base to collaborate with international efforts such as Enrol-HD study.

AUTHOR CONTRIBUTIONS

Conceptualization and design: Mendi J Muthinja and Mie Rizig. Data acquisition: All authors. Drafting of manuscript: Mendi J Muthinja and Mie Rizig. Critical revision of manuscript for intellectual content: All authors. Statistical analysis: Mendi J Muthinja and Mie Rizig. Administrative, technical, or material support: Mendi J Muthinja and Mie Rizig. Supervision of genotyping: Mendi J Muthinja and Mie Rizig. Data management: Mendi J Muthinja and Mie Rizig.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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DATA AVAILABILITY STATEMENT

The data that support 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.

Data availability statement anonymous data can be obtained by bona fide researchers from the corresponding author upon request. However, due to data confidentiality, certain clinical data that could potentially identify participants or their families may not be included.

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